CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 77-538

Name: Fluticasone Propionate Nasal Spray, 0.05 mg (50 micrograms)/spray, packaged in 120 metered spray container.

Sponsor: Apotex, Inc.

Approval Date: September 12, 2007

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-538

CONTENTS

Reviews / Information Included in this Review

Approval Letter	**X**
Tentative Approval Letter	
Labeling	**X**
Labeling Reviews	**X**
Medical Review	
Chemistry Reviews	**X**
Bioequivalence Review	**X**
Statistical Review	
Microbiology Review	
Administrative & Correspondence Documents	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

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ANDA 77-538

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 77-538

Apotex Corp.
Attention: Kiran Krishnan, MPharm, RAC
Manager, Regulatory Affairs, and
U.S. Agent for Apotex Inc.
2400 North Commerce Parkway, Suite 400
Weston, FL 33326

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated February 28, 2005, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Fluticasone Propionate Nasal Spray, 0.05 mg (50 micrograms)/spray, packaged in 120 metered spray containers.

Reference is also made to your amendments dated May 26, August 12, August 30, and November 8, 2005; March 22, April 5, April 20, April 25, and April 28, May 26, June 13 and June 23, July 18, July 20, August 30, and October 17, 2006; and January 15, April 12, and August 14, 2007.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Fluticasone Propionate Nasal Spray, 0.05 mg (50 micrograms)/spray, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug, Flonase Nasal Spray, 0.05 mg (50 micrograms)/spray, of GlaxoSmithKline.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert L. West
9/12/2007 09:28:05 AM
for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-538

LABELING

250151

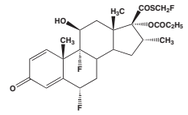
PRESCRIBING INFORMATION
℞ Only

Fluticasone Propionate Nasal Spray 50 mcg

For Intranasal Use Only
SHAKE GENTLY BEFORE USE

DESCRIPTION

Fluticasone p opionate, he active component of fluticasone p opionate nasal spray, is a syn hetic corticoste oid having the chemical name S-(fluo omethyl)6α,9-difluo o-11β-17-d hyd oxy-16α-methyl-3-oxoand osta-1,4-diene-17β-ca bo hioate, 17-propionate and the following chemical structure:



Fluticasone propionate is a white or almost white, crystalline powder wi h a molecular weight of 500.6, and the molecular formula is $C_{25}H_{31}F_3O_5S$. It is practically insoluble in water, f eely soluble in dime hylformamide, sparingly soluble in acetone and in dichloromethane and slightly soluble in e hanol (95%).

Fluticasone p opionate nasal spray, 50 mcg is an aqueous suspension of mic ofine fluticasone p opionate for topical administration to he nasal mucosa by means of a metering, atomizing spray pump. Fluticasone p opionate nasal spray also contains 0.02% w/w benzalkonium chloride, dext ose, microcrystalline cellulose and carboxymethylcellulose sodium, 0.25% w/w phenyle hyl alcohol, polysorbate 80, purified water, and has a pH between 5 and 7.

It is necessary to prime he pump before first use or after a period of non use (1 week or more). After initial priming (6 actuations), each actuation delivers 50 mcg of fluticasone p opionate in 100 mg of formulation h ough he nasal adapter. Each 16 g bottle of fluticasone p opionate nasal spray p ovides 120 metered sprays. After 120 metered sprays, the amount of fluticasone p opionate delivered per actuation may not be consistent and he unit should be discarded.

CLINICAL PHARMACOLOGY

Mechanism of Action

Fluticasone propionate is a syn hetic, trifluorinated corticoste oid wi h anti-inflammatory activity. *In vitro* dose esponse studies on a cloned human glucocorticoid receptor system involving binding and gene expression afforded 50% responses at 1.25 and 0.17 nM concentrations, respectively. Fluticasone p opionate was 3-fold to 5-fold more potent than dexamethasone in these assays. Data f om he McKenzie vasoconstrictor assay in man also support its potent glucocorticoid activity.

In preclinical studies, fluticasone propionate revealed p ogeste one-like activity similar to he natural hormone. However, the clinical significance of these findings in relation to the low plasma levels (*see* **Pharmacokinetics**) is not known.

The p ecise mechanism through which fluticasone propionate affects allergic hinitis symptoms is not known. Corticosteroids have been shown to have a wide range of effects on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation. In 7 trials in adults, fluticasone propionate nasal spray has dec eased nasal mucosal eosinophils in 66% (35% for placebo) of patients and basophils in 39% (28% for placebo) of patients. The direct elationship of hese findings to long-term symptom relief is not known.

Fluticasone p opionate nasal spray, like o her corticoste oids, is an agent that does not have an immediate effect on allergic symptoms. A decrease in nasal symptoms has been noted in some patients 12 hours after initial treatment wi h fluticasone p opionate nasal spray. Maximum benefit may not be reached for several days. Similarly, when corticoste oids a e discontinued, symptoms may not retu n for several days.

Pharmacokinetics

Absorption: The activity of fluticasone propionate nasal spray is due to the parent drug, fluticasone propionate. Indirect calculations indicate that fluticasone propionate delivered by he intranasal route has an absolute bioavailability averaging less than 2%. After intranasal treatment of patients w th allergic hinitis for 3 weeks, fluticasone propionate plasma concentrations we e above he level of detection (50 pg/mL) only when recommended doses were exceeded and then only in occasional samples at low plasma levels. Due to he low bioavailability by he intranasal route, he majority of the pharmacokinetic data was obtained via o her routes of administration. Studies using oral dosing of radiolabeled drug have demonstrated hat fluticasone propionate is highly extracted from plasma and absorption is low. Oral bioavailability is negligible, and the majority of the circulating radioactivity is due to an inactive metabolite.

Distribution: Following intravenous administration, he initial disposition phase for fluticasone p opionate was rapid and consistent w th its high lipid solubility and tissue binding. The volume of distribution averaged 4.2 L/kg.

The percentage of fluticasone p opionate bound to human plasma p oteins averaged 91% wi h no obvious concentration relationship. Fluticasone p opionate is weakly and reversibly bound to eryth ocytes and freely equilibrates between ery h ocytes and plasma. Fluticasone p opionate is not significantly bound to human transcortin.

Metabolism: The total blood clearance of fluticasone propionate is high (average, 1,093 mL/min), wi h renal clearance accounting for less than 0.02% of he total. The only circulating metabolite detected in man is he 17β-carboxylic acid derivative of fluticasone p opionate, which is formed th ough the cytochrome P450 3A4 pathway. This inactive metabolite had less affinity (app oximately 1/2,000) han he parent drug for the glucocorticoid receptor of human lung cytosol *in vitro* and negligible pharmacological activity in animal studies. Other metabolites detected *in vitro* using cultured human hepatoma cells have not been detected in man.

Elimination: Following intravenous dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7 8 hours. Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, w th the remainder excreted in the feces as pa ent drug and metabolites.

Special Populations

Fluticasone propionate nasal spray was not studied in any special populations, and no gender-specific pharmacokinetic data have been obtained.

Drug Interactions

Fluticasone p opionate is a substrate of cytoch ome P450 3A4. Coadministration of fluticasone p opionate and he highly potent cytoch ome P450 3A4 inhibitor ritonavir is not recommended based upon a multiple dose, c ossover drug interaction study in 18 heal hy subjects. Fluticasone p opionate aqueous nasal spray (200 mcg once daily) was coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone p opionate concentrations following fluticasone p opionate aqueous nasal spray alone were undetectable (<10 pg/mL) in most subjects, and when concentrations were detectable peak levels (C_{max} averaged 11.9 pg/mL [range, 10.8 to 14.1 pg/mL] and $AUC_{(0\text{-}\tau)}$ averaged 8.43 pg hr/mL [range, 4.2 to 18.8 pg·hr/mL]). Fluticasone p opionate C_{max} and $AUC_{(0\text{-}\tau)}$ increased to 318 pg/mL (range, 110 to 648 pg/mL) and 3,102.6 pg·hr/mL (range, 1,207.1 to 5,662.0 pg hr/mL), respectively, after coadministration of ritonavir with fluticasone p opionate aqueous nasal spray. This significant increase in plasma fluticasone p opionate exposure resulted in a significant decrease (86%) in plasma cortisol area under he plasma concentration versus time curve (AUC).

Caution should be exercised when o her potent cytochrome P450 3A4 inhibitors are coadministered wi h fluticasone propionate. In a drug interaction study, coadministration of orally inhaled fluticasone propionate (1,000 mcg) and ketoconazole (200 mg once daily) esulted in increased fluticasone propionate exposure and reduced plasma cortisol AUC, but had no effect on urinary excretion of cortisol.

In ano her multiple-dose drug interaction study, coadministration of orally inhaled fluticasone propionate (500 mcg twice daily) and ery hromycin (333 mg 3 times daily) did not affect fluticasone propionate pharmacokinetics.

Pharmacodynamics

In a trial to evaluate the potential systemic and topical effects of fluticasone p opionate nasal spray on allergic hinitis symptoms, he benefits of comparable drug blood levels p oduced by fluticasone p opionate nasal spray and oral fluticasone propionate were compared. The doses used were 200 mcg of fluticasone p opionate nasal spray, he nasal spray vehicle (plus oral placebo), and 5 and 10 mg of oral fluticasone p opionate (plus nasal spray vehicle) per day for 14 days. Plasma levels were undetectable in he majority of patients after intranasal dosing, but present at low levels in he majority after oral dosing. Fluticasone p opionate nasal spray was significantly more effective in reducing symptoms of allergic hinitis than either the oral fluticasone p opionate or he nasal vehicle. This trial demonstrated hat the herapeutic effect of fluticasone p opionate nasal spray can be attributed to he topical effects of fluticasone p opionate.

In another trial, the potential systemic effects of fluticasone p opionate nasal spray on the hypothalamic-pituitary-adrenal (HPA) axis were also studied in allergic patients. Fluticasone p opionate nasal spray given as 200 mcg once daily or 400 mcg twice daily was compared wi h placebo or oral prednisone 7.5 or 15 mg given in he morning. Fluticasone p opionate nasal spray at ei her dose for 4 weeks did not affect he adrenal response to 6-hour cosyntropin stimulation, while bo h doses of oral prednisone significantly reduced he response to cosyntropin.

Clinical Trials

A total of 13 randomized, double-blind, parallel-g oup, multicenter, vehicle placebo-cont olled clinical trials were conducted in he United States in adults and pediatric patients (4 years of age and older) to investigate regular use of fluticasone p opionate nasal spray in patients w th seasonal or perennial allergic hinitis. The trials included 2,633 adults (1,439 men and 1,194 women) wi h a mean age of 37 (range, 18 to 79 years). A total of 440 adolescents (405 boys and 35 girls), mean age of 14 (range, 12 to 17 years), and 500 children (325 boys and 175 girls), mean age of 9 (range, 4 to 11 years) were also studied. The overall racial distribution was 89% white, 4% black, and 7% o her. These trials evaluated he total nasal symptom scores (TNSS) that included hinor hea, nasal obstruction, sneezing, and nasal itching in known allergic patients who were treated for 2 to 24 weeks. Subjects treated w th fluticasone propionate nasal spray exhibited significantly greater decreases in TNSS than vehicle placebo-treated patients. Nasal mucosal basophils and eosinophils were also reduced at he end of treatment in adult studies; however, he clinical significance of this decrease is not known.

There were no significant differences between fluticasone p opionate regimens whether administered as a single daily dose of 200 mcg (two 50 mcg sprays in each nostril) or as 100 mcg (one 50 mcg spray in each nostril) twice daily in 6 clinical trials. A clear dose response could not be identified in clinical trials. In 1 trial, 200 mcg/day was slightly more effective than 50 mcg/day during he first few days of treatment; hereafter, no difference was seen.

Two randomized, double-blind, parallel-g oup, multicenter, vehicle placebo-cont olled 28-day trials were conducted in the United States in 732 patients (243 given fluticasone p opionate) 12 years of age and older to investigate “as-needed” use of fluticasone p opionate nasal spray (200 mcg) in patients with seasonal allergic hinitis. Patients were instructed to take he study medication only on days when hey hought hey needed he medication for symptom cont ol, not to exceed 2 sprays per nostril on any day, and not more han once daily. “As-needed” use was p ospectively defined as average use of study medication no more han 75% of study days. Average use of study medications was 57% to 70% of days for all treatment arms. The studies demonstrated significantly greater reduction in TNSS (sum of nasal congestion, hinor hea, sneezing, and nasal itching) wi h fluticasone p opionate nasal spray 200 mcg compared to placebo. The relative difference in efficacy with as-needed use as compared to regularly administered doses was not studied.

Three randomized, double-blind, parallel-g oup, vehicle placebo-cont olled trials were conducted in 1,191 patients to investigate regular use of fluticasone p opionate nasal spray in patients wi h perennial nonallergic hinitis. These trials evaluated the patient-rated TNSS (nasal obstruction, postnasal drip, hinor hea) in patients treated for 28 days of double-blind herapy and in 1 of he 3 trials for 6 months of open-label treatment. Two of these trials demonstrated hat patients treated wi h fluticasone p opionate nasal spray at a dose of 100 mcg twice daily exhibited statistically significant decreases in TNSS compared wi h patients treated wi h vehicle.

Individualization of Dosage

Patients should use fluticasone propionate nasal spray at regular intervals for optimal effect.

Adult patients may be started on a 200 mcg once-daily regimen (two 50 mcg sprays in each nostril once daily). An alte native 200 mcg/day dosage regimen can be given as 100 mcg twice daily (one 50 mcg spray in each nostril twice daily).

Individual patients will experience a variable time to onset and different degree of symptom relief. In 4 randomized, double-blind, vehicle placebo cont olled, parallel-g oup allergic hinitis studies and 2 studies of patients in an outdoor “park” setting (park studies), a decrease in nasal symptoms in treated subjects compared to placebo was shown to occur as soon as 12 hours after treatment w th a 200 mcg dose of fluticasone p opionate nasal spray. Maximum effect may take several days. Regular-use patients who have responded may be able to be maintained (after 4 to 7 days) on 100 mcg/day (1 spray in each nostril once daily).

Some patients (12 years of age and older) with seasonal allergic hinitis may find as-needed use of fluticasone p opionate nasal spray (not to exceed 200 mcg daily) effective for symptom control (see Clinical Trials). Greater symptom cont ol may be achieved wi h scheduled regular use. Efficacy of as-needed use of fluticasone p opionate nasal spray has not been studied in pediatric patients under 12 years of age with seasonal allergic hinitis, or patients w th perennial allergic or nonallergic hinitis.

Pediatric patients (4 years of age and older) should be started wi h 100 mcg (1 spray in each nostril once daily). Treatment wi h 200 mcg (2 sprays in each nostril once daily or 1 spray in each nostril twice daily) should be reserved for pediatric patients not adequately responding to 100 mcg daily. Once adequate cont ol is achieved, the dosage should be decreased to 100 mcg (1 spray in each nostril) daily.

Maximum total daily doses should not exceed 2 sprays in each nostril (total dose, 200 mcg/day). There is no evidence that exceeding he recommended dose is more effective.

INDICATIONS AND USAGE

Fluticasone propionate nasal spray is indicated for the management of he nasal symptoms of seasonal and perennial allergic and nonallergic hinitis in adults and pediatric patients 4 years of age and older.

Safety and effectiveness of fluticasone p opionate nasal spray in children below 4 years of age have not been adequately established.

CONTRAINDICATIONS

Fluticasone propionate nasal spray is contraindicated in patients with a hypersensitivity to any of its ingredients.

WARNINGS

The replacement of a systemic corticoste oid with a topical corticoste oid can be accompanied by signs of adrenal insufficiency, and in addition some patients may experience symptoms of wi hdrawal, e.g., joint and/or muscular pain, lassitude, and depression. Patients previously treated for p olonged periods w th systemic corticoste oids and transferred to topical corticoste oids should be carefully monitored for acute adrenal insufficiency in response to stress. In hose patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, too rapid a decrease in systemic corticoste oids may cause a severe exacerbation of their symptoms.

The concomitant use of intranasal corticoste oids wi h o her inhaled corticoste oids could increase he risk of signs or symptoms of hypercorticism and/or suppression of he HPA axis.

A drug interaction study in healthy subjects has shown hat ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can significantly increase plasma fluticasone p opionate exposure, resulting in significantly reduced serum cortisol concentrations (*see* **CLINICAL PHARMACOLOGY: Drug Interactions** *and* **PRECAUTIONS: Drug Interactions**). During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticoste oid effects including Cushing synd ome and adrenal suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not recommended unless he potential benefit to the patient outweighs he risk of systemic corticoste oid side effects.

Persons who are using drugs hat suppress he immune system are more susceptible to infections han heal hy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticoste oids. In children or adults who have not had hese diseases or been p operly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticoste oid administration affect he risk of developing a disseminated infection is not known. The contribution of he underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, p ophylaxis wi h varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, p ophylaxis w th pooled intramuscular immunoglobulin (IG) may be indicated. (See he respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment w th antiviral agents may be conside ed.

Avoid spraying in eyes.

PRECAUTIONS

General

Intranasal corticoste oids may cause a reduction in g ow th velocity when administered to pediatric patients (*see* **PRECAUTIONS: Pediatric Use**).

Rarely, immediate hypersensitivity reactions or contact dermatitis may occur after the administration of fluticasone p opionate nasal spray. Rare instances of wheezing, nasal septum perforation, cataracts, glaucoma, and increased intraocular pressure have been reported following the intranasal application of corticoste oids, including fluticasone p opionate.

Use of excessive doses of corticoste oids may lead to signs or symptoms of hypercorticism and/or suppression of HPA function.

Al hough systemic effects have been minimal w th recommended doses of fluticasone p opionate nasal spray, potential risk increases wi h larger doses. Therefore, larger han recommended doses of fluticasone p opionate nasal spray should be avoided.

When used at higher han recommended doses or in rare individuals at recommended doses, systemic corticoste oid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, he dosage of fluticasone p opionate nasal spray should be discontinued slowly consistent wi h accepted

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Patient Leaflet
℞ Only

Fluticasone Propionate Nasal Spray 50 mcg

Please read this patient leaflet carefully before you start to take your medicine. It p ovides a summary of information on your medicine.

For further information ask your doctor or pharmacist.

WHAT YOU SHOULD KNOW ABOUT RHINITIS

Rhinitis is a word that means inflammation of he lining of he nose. If you suffer f om hinitis, your nose becomes stuffy and runny. Rhinitis can also make your nose itchy, and you may sneeze a lot. Rhinitis can be caused by allergies to pollen, animals, molds, or other materials - or it may have a nonallergic cause.

WHAT YOU SHOULD KNOW ABOUT FLUTICASONE PROPIONATE NASAL SPRAY

Your doctor has prescribed fluticasone p opionate nasal spray, a medicine that can help treat your hinitis. Fluticasone p opionate nasal spray contains fluticasone p opionate, which is a syn hetic corticoste oid. Corticoste oids are natural substances found in the body hat help fight inflammation. When you spray fluticasone p opionate nasal spray into your nose, it helps to reduce he symptoms of allergic reactions and he stuffiness, runniness, itching, and sneezing that can bo her you.

THINGS TO REMEMBER ABOUT FLUTICASONE PROPIONATE NASAL SPRAY

1. Shake gently before using.
2. Use your nasal spray as directed by your doctor. The directions are on he pharmacy label.
3. Keep your nasal spray **out of the reach of children.**

BEFORE USING YOUR NASAL SPRAY

- If you are pregnant (or intending to become pregnant),
- If you are breastfeeding a baby,
- If you are allergic to fluticasone p opionate nasal spray or any other nasal corticoste oid,
- If you are taking a medicine containing ritonavir (commonly used to treat HIV infection or AIDS)

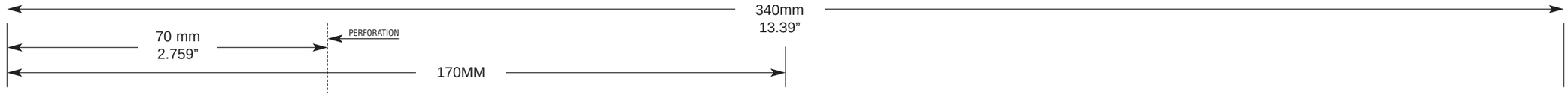
Tell your doctor before starting to take this medicine. In some circumstances, his medicine may not be suitable and your doctor may wish to give you a different medicine. Make sure hat your doctor knows what o her medicines you are taking.

USING YOUR NASAL SPRAY

- Follow he instructions shown in the rest of his patient leaflet. If you have any p oblems, tell your doctor or pharmacist.
- It is important that you use it as directed by your doctor. The pharmacist’s label will usually tell you what dose to take and how often. If it doesn’t, or you are not sure, ask your doctor or pharmacist.

DOSAGE

- For **ADULTS,** the usual starting dosage is ***2 sprays in each nostril*** **once daily.** Sometimes your doctor may recommend using 1 spray in each nostril twice a day (mo ning and evening). You should not use more than a total of 2 sprays in each nostril daily. After you have begun to feel better, 1 spray in each nostril daily may be adequate for you.
- For **ADOLESCENTS and CHILDREN** (4 years of age and older), he usual starting dosage is ***1 spray in each nostril once daily.*** Sometimes your doctor may recommend using 2 sprays in each nostril daily. Then, after you have begun to feel better, 1 spray in each nostril daily may be adequate for you.
- DO NOT use more of your medicine or take it more often han your doctor advises.
- Fluticasone p opionate nasal spray may begin to work wi hin 12 hours of he first dose, but it takes several days of regular use to reach its greatest effect. It is important hat you use fluticasone p opionate nasal spray as prescribed by your doctor. Best results will be obtained by using the spray on a regular basis. If symptoms disappear, contact your doctor for further instructions.
- If you also have itchy, watery eyes, you should tell your doctor. You may be given an additional medicine to treat your eyes. Be careful not to confuse them, particularly if the second medicine is an eye drop.
- If you miss a dose, just take your regularly scheduled next dose when it is due. DO NOT DOUBLE he dose.

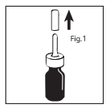


HOW TO USE YOUR NASAL SPRAY
Read he complete instructions carefully and use only as directed.

BEFORE USING

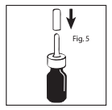
1. Shake he bottle gently and then emove the translucent cap (Fig. 1).
2. It is necessary to prime he pump into the air the first time it is used, or when you have not used it for a week or more. To prime he pump, hold the bottle as shown w th he nasal applicator pointing away from you and w th your forefinger and middle finger on ei her side of the nasal applicator and your thumb unde neath he bottle. When you prime he pump for the first time, press down and release the pump 6 times. (Fig. 2).

   The pump is now ready for use. If he pump is not used for 7 days, prime until a fine spray appears.



USING THE SPRAY

3. Blow your nose to clear your nostrils.
4. Close one nostril. Tilt your head forward slightly and, keeping the bottle upright, carefully insert he nasal applicator into he other nostril (Fig. 3).
5. Start to brea he in th ough your nose, and WHILE BREATHING IN press firmly and quickly down once on the applicator to release the spray. To get a full actuation, use your forefinger and middle finger to spray while supporting the base of the bottle wi h your thumb. Avoid spraying in eyes. Breathe gently inwards th ough he nostril (Fig. 4).
6. Brea he out th ough your mou h.
7. If a second spray is required in that nostril, repeat steps 4 th ough 6.
8. Repeat steps 4 h ough 7 in he other nostril.
9. Wipe he nasal applicator with a clean tissue and replace the translucent cap (Fig. 5).
10. Do not use this bottle for more han he labeled number of sprays even though he bottle is not completely empty. Before you throw he bottle away, you should consult your doctor to see if a refill is needed. Do not take extra doses or stop taking fluticasone propionate nasal spray without consulting your doctor.



CLEANING
Your nasal spray should be cleaned at least once a week. To do his:

1. Remove he translucent cap and then gently pull upwards to free he nasal applicator.
2. Wash the applicator and translucent cap under warm tap water. Allow to dry at oom temperature, then place he applicator and translucent cap back on the bottle.
3. If he nasal applicator becomes blocked, it can be removed as above and left to soak in warm water. Rinse with cold tap water, dry, and refit. **Do not try to unblock the nasal applicator by inserting a pin or other sharp object.**

STORING YOUR NASAL SPRAY

- Keep your fluticasone propionate nasal spray **out of the reach of children.**
- Avoid spraying in eyes.
- **Store between 20° - 25°C (68° - 77°F) [See USP Controlled Room Temperature].**
- Do not use your fluticasone p opionate nasal spray after he expiry date shown on the label or box.

REMEMBER: This medicine has been prescribed for you by your doctor. DO NOT give this medicine to anyone else.

FURTHER INFORMATION
This patient leaflet does not contain he complete information about your medicine. *If you have any questions, or are not sure about something, then you should ask your doctor or pharmacist.*

You may want to read his patient leaflet again. Please DO NOT THROW IT AWAY until you have finished your medicine.

Manufactured by:
Apotex Inc.
To onto, Ontario
Canada M9L 1T9

Manufactured for:
Apotex Corp.
Weston, FL
33326

250151 October 2006

procedures for discontinuing oral corticoste oid herapy.

In clinical studies wi h fluticasone p opionate administered intranasally, the development of localized infections of he nose and pharynix w th *Candida albicans* has occurred only rarely. When such an infection develops, it may require treatment wi h app opriate local therapy and discontinuation of treatment w th fluticasone p opionate nasal spray. Patients using fluticasone p opionate nasal spray over several mon hs or longer should be examined periodically for evidence of *Candida* infection or o her signs of adverse effects on he nasal mucosa.

Intranasal corticoste oids should be used with caution, if at all, in patients w th active or quiescent tuberculous infections of he respiratory tract; untreated local or systemic fungal or bacterial infections; systemic viral or parasitic infections; or ocular herpes simplex.

Because of he inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septal ulcers, nasal surgery, or nasal trauma should not use a nasal corticoste oid until healing has occurred.

Information for Patients
Patients being treated wi h fluticasone p opionate nasal spray should receive the following information and instructions. This information is intended to aid them in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Patients should be wa ned to avoid exposure to chickenpox or measles and, if exposed, to consult heir physician w thout delay.

Patients should use fluticasone p opionate nasal spray at regular intervals for optimal effect. Some patients (12 years of age and older) wi h seasonal allergic hinitis may find as-needed use of 200 mcg once daily effective for symptom cont ol (*see* **Clinical Trials**).

A decrease in nasal symptoms may occur as soon as 12 hours after starting therapy wi h fluticasone p opionate nasal spray. Results in several clinical trials indicate statistically significant improvement w thin the first day or two of treatment; however, the full benefit of fluticasone p opionate nasal spray may not be achieved until treatment has been administered for several days. The patient should not increase he prescribed dosage but should contact he physician if symptoms do not imp ove or if he condition worsens.

For the p oper use of fluticasone p opionate nasal spray and to attain maximum imp ovement, he patient should read and follow carefully he patient leaflet accompanying he p oduct.

Drug Interactions
Fluticasone p opionate is a substrate of cytoch ome P450 3A4. A drug interaction study wi h fluticasone propionate aqueous nasal spray in healthy subjects has shown that ritonavir (a highly potent cytoch ome P450 3A4 inhibitor) can significantly increase plasma fluticasone p opionate exposure, resulting in significantly reduced serum cortisol concentrations (*see* **CLINICAL PHARMACOLOGY: Drug Interactions**). During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone p opionate and ritonavir, resulting in systemic corticoste oid effects including Cushing syndrome and adrenal suppression. Therefore, coadministration of fluticasone p opionate and ritonavir is not recommended unless the potential benefit to the patient outweighs he risk of systemic corticoste oid side effects.

In a placebo-cont olled, c ossover study in 8 heal hy volunteers, coadministration of a single dose of orally inhaled fluticasone p opionate (1,000 mcg; 5 times the maximum daily intranasal dose) with multiple doses of ketoconazole (200 mg) to steady state resulted in increased plasma fluticasone p opionate exposure, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol. Caution should be exercised when fluticasone p opionate nasal spray is coadministered with ketoconazole and o her known potent cytoch ome P450 3A4 inhibitors.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1,000 mcg/kg (app oximately 20 times he maximum recommended daily intranasal dose in adults and app oximately 10 times the maximum recommended daily intranasal dose in children on a mcg/m^2 basis) for 78 weeks or in rats at inhalation doses up to 57 mcg/kg (app oximately 2 times the maximum recommended daily intranasal dose in adults and app oximately equivalent to the maximum recommended daily intranasal dose in children on a mcg/m^2 basis) for 104 weeks.

Fluticasone p opionate did not induce gene mutation in p okaryotic or eukaryotic cells *in vitro.* No significant clastogenic effect was seen in cultured human peripheral lymphocytes *in vitro* or in he mouse mic onucleus test.

No evidence of impairment of fertility was observed in rep oductive studies conducted in male and female rats at subcutaneous doses up to 50 mcg/kg (app oximately 2 times the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis). P ostate weight was significantly reduced at a subcutaneous dose of 50 mcg/kg.

Pregnancy
Teratogenic Effects: Pregnancy Catego y C. Subcutaneous studies in he mouse and rat at 45 and 100 mcg/kg, respectively (app oximately equivalent to and 4 times he maximum recommended daily intranasal dose in adults on a mcg/m^2 basis, respectively) revealed fetal toxicity characteristic of potent corticoste oid compounds, including embryonic g owth retardation, omphalocele, cleft palate, and retarded cranial ossification.

In the rabbit, fetal weight eduction and cleft palate were observed at a subcutaneous dose of 4 mcg/kg (less than the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis). However, no teratogenic effects were reported at oral doses up to 300 mcg/kg (approximately 25 times he maximum ecommended daily intranasal dose in adults on a mcg/m^2 basis) of fluticasone propionate to the rabbit. No fluticasone propionate was detected in he plasma in this study, consistent wi h the established low bioavailability following oral administration (*see* **CLINICAL PHARMACOLOGY**).

Fluticasone propionate crossed he placenta following oral administration of 100 mcg/kg to rats or 300 mcg/kg to rabbits (app oximately 4 and 25 times, respectively, he maximum recommended daily intranasal dose in adults on a mcg/m^2 basis).

There are no adequate and well-cont olled studies in pregnant women. Fluticasone p opionate should be used during pregnancy only if he potential benefit justifies the potential risk to he fetus.

Experience with oral corticoste oids since their int oduction in pharmacologic, as opposed to physiologic, doses suggests hat odents are more p one to teratogenic effects f om corticoste oids than humans. In addition, because here is a natural increase in corticoste oid p oduction during pregnancy, most women will require a lower exogenous corticoste oid dose and many will not need corticoste oid treatment during pregnancy.

Nursing Mothers
It is not known whether fluticasone p opionate is excreted in human breast milk. However, other corticoste oids have been detected in human milk. Subcutaneous administration to lactating rats of 10 mcg/kg of tritiated fluticasone p opionate (less than he maximum recommended daily intranasal dose in adults on a mcg/m^2 basis) resulted in measurable radioactivity in the milk. Since there are no data f om cont olled trials on he use of intranasal fluticasone p opionate by nursing mothers, caution should be exercised when fluticasone p opionate nasal spray is administered to a nursing woman.

Pediatric Use
Five hund ed (500) patients aged 4 to 11 years and 440 patients aged 12 to 17 years were studied in US clinical trials with fluticasone p opionate nasal spray. The safety and effectiveness of fluticasone p opionate nasal spray in children below 4 years of age have not been established.

Controlled clinical studies have shown hat intranasal corticosteroids may cause a eduction in grow h velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of HPA axis suppression, suggesting hat grow h velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients han some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with intranasal corticosteroids, including he impact on final adult height, are unknown. The potential for "catch-up" grow h following discontinuation of treatment w th intranasal corticosteroids has not been adequately studied. The grow h of pediatric patients eceiving intranasal corticosteroids, including fluticasone propionate nasal spray, should be monitored routinely (e.g., via stadiometry). The potential growth effects of prolonged treatment should be weighed against he clinical benefits obtained and he risks/benefits of treatment alternatives. To minimize he systemic effects of intranasal corticosteroids, including fluticasone propionate nasal spray, each patient should be titrated to he lowest dose hat effectively controls his/her symptoms.

A 1-year placebo-cont olled clinical g ow h study was conducted in 150 pediatric patients (ages 3 to 9 years) to assess he effect of fluticasone p opionate nasal spray (single daily dose of 200 mcg, the maximum app oved dose) on g owth velocity. F om he primary population of 56 patients receiving fluticasone p opionate nasal spray and 52 receiving placebo, the point estimate for g ow h velocity wi h fluticasone p opionate nasal spray was 0.14 cm/year lower han that noted wi h placebo (95% confidence interval ranging f om 0.54 cm/year lower than placebo to 0.27 cm/year higher han placebo). Thus, no statistically significant effect on g ow h was noted compared to placebo. No evidence of clinically relevant changes in HPA axis function or bone mineral density was observed as assessed by 12 hour urinary cortisol excretion and dual-energy x-ray absorptiometry, respectively.

The potential for fluticasone p opionate nasal spray to cause g owth suppression in susceptible patients or when given at higher doses cannot be ruled out.

Geriatric Use
A limited number of patients 65 years of age and older (n = 129) or 75 years of age and older (n = 11) have been treated wi h fluticasone p opionate nasal spray in US and non-US clinical trials. While he number of patients is too small to permit separate analysis of efficacy and safety, he adverse reactions reported in his population were similar to hose reported by younger patients.

ADVERSE REACTIONS
In controlled US studies, more than 3,300 patients wi h seasonal allergic, perennial allergic, or perennial nonallergic hinitis received treatment with intranasal fluticasone propionate. In general, adverse reactions in clinical studies have been primarily associated wi h irritation of he nasal mucous membranes, and he adverse reactions were reported w th approximately he same f equency by patients treated wi h he vehicle itself. The complaints did not usually interfere wi h treatment. Less han 2% of patients in clinical trials discontinued because of adverse events; his rate was similar for vehicle placebo and active comparators.

Systemic corticosteroid side effects were not reported during controlled clinical studies up to 6 months' duration wi h fluticasone propionate nasal spray. If recommended doses a e exceeded, however, or if individuals are particularly sensitive or taking fluticasone propionate nasal spray in conjunction wi h administration of other corticosteroids, symptoms of hypercorticism, e.g., Cushing syndrome, could occur.

The following incidence of common adverse reactions (>3%, where incidence in fluticasone propionate-treated subjects exceeded placebo) is based upon 7 controlled clinical trials in which 536 patients (57 girls and 108 boys aged 4 to 11 years, 137 female and 234 male adolescents and adults) we e treated wi h fluticasone propionate nasal spray 200 mcg once daily over 2 to 4 weeks and 2 controlled clinical trials in which 246 patients (119 female and 127 male adolescents and adults) were treated wi h fluticasone p opionate nasal spray 200 mcg once daily over 6 mon hs. Also included in he table are adverse events f om 2 studies in which 167 children (45 girls and 122 boys aged 4 to 11 years) were treated wi h fluticasone p opionate nasal spray 100 mcg once daily for 2 to 4 weeks.

Overall Adverse Experiences With > 3% Incidence on Fluticasone Propionate in Controlled Clinical Trials With Fluticasone Propionate Nasal Spray in Patients ≥ 4 Years With Seasonal or Perennial Allergic Rhinitis

Adverse Experience	Vehicle Placebo (n = 758) %	Fluticasone Propionate 100 mcg Once Daily (n = 167) %	Fluticasone Propionate 200 mcg Once Daily (n = 782) %
Headache	14.6	6.6	16.1
Pharyngitis	7.2	6.0	7.8
Epistaxis	5.4	6.0	6.9
Nasal bu ning/nasal irritation	2.6	2.4	3.2

Overall Adverse Experiences With > 3% Incidence on Fluticasone Propionate in Controlled Clinical Trials With Fluticasone Propionate Nasal Spray in Patients ≥ 4 Years With Seasonal or Perennial Allergic Rhinitis *(cont'd)*

Adverse Experience	Vehicle Placebo (n = 758) %	Fluticasone Propionate 100 mcg Once Daily (n = 167) %	Fluticasone Propionate 200 mcg Once Daily (n = 782) %
Nausea/vomiting	2.0	4.8	2.6
Asthma symptoms	2.9	7.2	3.3
Cough	2.8	3.6	3.8

Other adverse events hat occurred in ≤ 3% but ≥1% of patients and that were more common wi h fluticasone propionate (wi h uncertain relationship to treatment) included: blood in nasal mucus, runny nose, abdominal pain, diar hea, fever, flu-like symptoms, aches and pains, dizziness, b onchitis.

Observed During Clinical Practice
In addition to adverse events reported f om clinical trials, he following events have been identified during postapproval use of intranasal fluticasone p opionate in clinical practice. Because hey are reported voluntarily f om a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either heir seriousness, frequency of reporting, or causal connection to fluticasone p opionate or a combination of these factors.

General: Hypersensitivity reactions, including angioedema, skin rash, edema of the face and tongue, pruritus, urticaria, b onchospasm, wheezing, dyspnea, and anaphylaxis/anaphylactoid reactions, which in rare instances were severe.

Ear, Nose, and Throat: Alteration or loss of sense of taste and/or smell and, rarely, nasal septal perforation, nasal ulcer, sore hroat, hroat irritation and dryness, cough, hoarseness, and voice changes.

Eye: Dryness and irritation, conjunctivitis, blurred vision, glaucoma, increased intraocular pressure, and cataracts.

Cases of g owth suppression have been reported for intranasal corticoste oids, including fluticasone p opionate (*see* **PRECAUTIONS: Pediatric Use**).

OVERDOSAGE
Ch onic overdosage may result in signs/symptoms of hypercorticism (*see* **PRECAUTIONS**). Intranasal administration of 2 mg (10 times he recommended dose) of fluticasone p opionate twice daily for 7 days to heal hy human volunteers was well tolerated. Single oral doses up to 16 mg have been studied in human volunteers wi h no acute toxic effects reported. Repeat oral doses up to 80 mg daily for 10 days in volunteers and repeat oral doses up to 10 mg daily for 14 days in patients were well tolerated. Adverse reactions were of mild or moderate severity, and incidences were similar in active and placebo treatment g oups. Acute overdosage with his dosage form is unlikely since 1 bottle of fluticasone p opionate nasal spray contains app oximately 8 mg of fluticasone p opionate.

The oral and subcutaneous median le hal doses in mice and rats were >1,000 mg/kg (>20,000 and >41,000 times, respectively, the maximum recommended daily intranasal dose in adults and >10,000 and >20,000 times, respectively, he maximum recommended daily intranasal dose in children on a mg/m^2 basis).

DOSAGE AND ADMINISTRATION
Patients should use fluticasone p opionate nasal spray at regular intervals for optimal effect.

Adults
The recommended starting dosage in adults is 2 sprays (50 mcg of fluticasone propionate each) in each nostril once daily (total daily dose, 200 mcg). The same dosage divided into 100 mcg given twice daily (e.g., 8 a.m. and 8 p.m.) is also effective. After he first few days, patients may be able to reduce heir dosage to 100 mcg (1 spray in each nostril) once daily for maintenance herapy. Some patients (12 years of age and older) w th seasonal alle gic hinitis may find as-needed use of 200 mcg once daily effective for symptom control (*see* **Clinical Trials**). Greater symptom control may be achieved wi h scheduled regular use.

Adolescents and Children (4 Years of Age and Older)
Patients should be started with 100 mcg (1 spray in each nostril once daily). Patients not adequately responding to 100 mcg may use 200 mcg (2 sprays in each nostril). Once adequate cont ol is achieved, he dosage should be decreased to 100 mcg (1 spray in each nostril) daily.

The maximum total daily dosage should not exceed 2 sprays in each nostril (200 mcg/day). (*See* **Individualization of Dosage** *and* **Clinical Trials** *sections.*)

Fluticasone p opionate nasal spray is not recommended for children under 4 years of age.

Directions for Use
An illustrated patient leaflet for proper use accompanies each package of fluticasone propionate nasal spray.

HOW SUPPLIED
Fluticasone P opionate Nasal Spray, 50 mcg is supplied in an amber glass bottle fitted with a silver metering nasal pump, white plastic actuator, and translucent cap in a box of 1 (NDC 60505-0829-1) wi h a package insert (prescribing information and patient leaflet) for use. Each bottle contains a net fill weight of 16 g and will p ovide 120 actuations. Each actuation delivers 50 mcg of fluticasone p opionate in 100 mg of formulation th ough he nasal adapter. The correct amount of medication in each spray cannot be assured after 120 sprays even though he bottle is not completely empty. The bottle should be discarded when the labeled number of actuations has been used.

Store at 20° - 25°C (68° - 77°F) [See USP Controlled Room Temperature]. Shake gently before each use.

Manufactured by:
Apotex Inc.
Toronto, Ontario
Canada M9L 1T9

Manufactured for:
Apotex Corp
Weston, FL
33326

250151 October 2006

APOTEX
ADVANCING GENERICS

PRINTED PACKAGING MATERIAL MASTER Copy of

Material Code: 280474	QA Rev#: 0	Description: CTNUSAFLUTICASONEN/SPRYUSP50MCG/SPRY120	
QA Change: N/A		C of A: N/A	CCF#:
Previous Code: 277207	Label Draft Date: N/A	Dimensions/Dieline#: 973E 40 mm x 40 mm x 122.5 mm (1.575" x 1.575" x 4.823")	Minimum Font Size: 9 pt
Pantone Colours	(b) (4)	(b) (4)	(b) (4) BLACK AQUEOUS COATING
Pre or Post Commercial Change:	Text changes as per RA - April 09		Effective Date:
Prepared by: (b) (6) Date: April 24, 2009	Customer Approval: Date:	QA Reviewed: Date:	QA Approval: Date:

280474

LOCATION OF LOT & EXP. 40 mm x 40 mm

973E

NDC 60505-0829-1
16 g net fill weight

Fluticasone Propionate Nasal Spray USP

50 mcg

50 mcg per spray

120 Metered Sprays

℞ Only

For Intranasal Use Only

APOTEX CORP.

Contains: An aqueous suspension containing fluticasone propionate and 0.02% w/w benzalkonium chloride, dextrose, microcrystalline cellulose and carboxymethylcellulose sodium, 0.25% w/w phenylethyl alcohol, polysorbate 80 and purified water. pH 5-7.

It is necessary to prime the pump before first use or after a period of non-use (1 week or more). After initial priming (6 actuations), each 100 mg spray delivered by the nasal adapter contains 50 mcg of fluticasone propionate.

Store at 20° - 25°C (68° - 77°F) [See USP Controlled Room Temperature].

Shake gently before each use.

ATTENTION PHARMACIST:
Detach Patient Instructions from Prescribing Information along perforation and dispense with prescription.

Important: Read accompanying directions carefully.

See Package Insert for Dosage and Administration.

SEE SIDE PANEL FOR CLEANING INSTRUCTIONS.

Manufactured by:
Apotex Inc.
Toronto, Ontario
Canada M9L 1T9

Manufactured for:
Apotex Corp.
Weston, FL 33326

IMPORTANT: Cleaning Instructions
Your nasal spray should be cleaned at least once a week. To do this:

1. Remove the translucent cap and then gently pull upwards to free the nasal applicator.
2. Wash the applicator and translucent cap under warm tap water. Allow to dry at room temperature, then place the applicator and translucent cap back on the bottle.
3. If the nasal applicator becomes blocked, it can be removed as above and left to soak in warm water. Rinse with cold tap water, dry, and refit. **Do not try to unblock the nasal applicator by inserting a pin or other sharp object.**

3 60505 08291 9

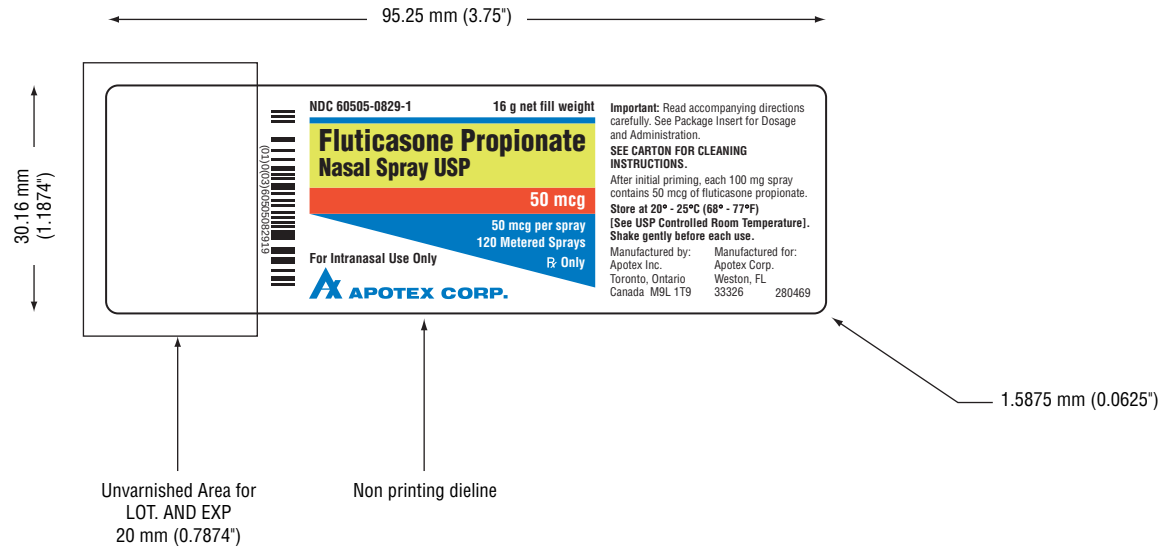
280474

APOTEX
ADVANCING GENERICS

PRINTED PACKAGING MATERIAL MASTER

Copy of

Material Code: 280469	QA Rev#: 0	Description: LBLUSAFLUTICASONEN/SPRYUSP50MCG/SPRY120	
QA Change: N/A		C of A: N/A	CCF#:
Previous Code: 277273	Label Draft Date: N/A	Dimensions/Dieline#: 30.16 mm x 95.25 mm (1.1874" x 3.75") CR 1.5875 mm (0.0625")	Minimum Font Size: 4.4 pt
Pantone Colours	(b) (4)	(b) (4)	(b) (4) BLACK UV VARNISH
Pre or Post Commercial Change:	Text changes as per RA - April 09		Effective Date:
Prepared by: (b) (6) Date: April 24, 2009	Customer Approval: Date:	QA Reviewed: Date:	QA Approval: Date:



Enlarged 200%

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-538

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 77-538

Date of Submission: **February 28, 2005**

Applicant's Name: Apotex, Inc.

Established Name: Fluticasone Propionate Nasal Spray, 50 mcg

Labeling Deficiencies:

1. **CONTAINER** (50 mcg) – Satisfactory in DRAFT.
2. **CARTON** *(50 mcg)* - Satisfactory in DRAFT.
3. **PATIENT INSTRUCTION**
   a. Revise "Please read this patient (b) (4) carefully before you start to take your medicine" to read "Please read this patient leaflet carefully before you start to take your medicine".
   b. ***USING YOUR NASAL SPRAY*** – Revise the first sentence in the first bullet point to read "Follow the instructions shown in the rest of this patient leaflet".
   c. ***FUTHER INFORMATION***: Revise the first sentence to read "This leaflet does not contain the complete information about your medicine
4. **INSERT** – Above the "DESCRIPTION" section add the statement "SHAKE GENTLY BEFORE USE."

Please revise your labeling, as instructed above, and submit each labeling piece in final print.

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidance for industry regarding electronic submissions: Providing Regulatory Submissions in Electronic Format — ANDAs (Issued 6/2002) (http://www.fda.gov/cder/guidance/5004fnl.htm). The guidance specifies labeling to be submitted in pdf format. To assist in our review, we request that labeling also be submitted in MS Word format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.fda.gov/cder/cdernew/listserv.html or
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		x	
Is this name different than that used in the Orange Book?			x
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels		x	

and labeling? Is "Jointly Manufactured by...", statement needed?			
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			x
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section? [not scored]			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?			x
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		x	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		x	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		x	

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. **MODEL LABELING** – The review was base on Flonase Nasal Spray, 50 mcg per spray, (NDA 20-121/S-030) approved on January 18, 2002. This supplement provides for the addition of a description of fluticasone propionate's interactions with ritonavir to the CLINICAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS sections of the package insert and to the Patient's Instructions for use leaflet.

2. This drug product is **not** the subject of a USP monograph.

3. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition section.

Strength (Label Claim):		50 mcg			
Component and Quality Standard (and Grade, if applicable)	Function of Component	Theoretical Quantity			
		Per Spray (mcg/100 mg)	Per Unit (g/16 g Bottle)	Concentration (g/kg)	%
Fluticasone Propionate BP	Active drug substance	50	(b) (4)		
Benzalkonium Chloride (b) (4) NF/EP ((b))					(b) (4)
Dextrose (b) (4) USP					
Microcrystalline Cellulose and Carboxymethyl-cellulose Sodium NF					
Phenylethyl Alcohol USP					
Polysorbate 80 NF (b) (4)					
Purified Water USP/EP					
TOTAL:		100 mg	16 g	1.0 kg	100.0%

4. PATENTS/EXCLUSIVITIES:

Patent Data – NDA 20-121

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
			There is no unexpired patent for this product.	II	

Exclusivity Data– NDA 20-121

Code	Reference	Expiration	Labeling Impact
PED	PEDIATRIC EXCLUSIVITY	**NOV 01,2006**	NONE
D-76	FOR USE ON AN "AS NEEDED" OR PRN BASIS FOR THE MANAGEMENT OF NASAL SYMPTOMS IN PATIENTS FOR WHOM THE DRUG IS INDICATED	**MAY 23,2005**	NONE
PED	PEDIATRIC EXCLUSIVITY	**NOV 23,2005**	NONE
M-24	INFORMATION ON RESULTS OF A LONG TERM LONGITUDINAL GROWTH STUDY AND PEDIATRIC SAFETY INFORMATION	**MAY 01,2006**	NONE

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

- USP: Preserve in tight, light-resistant containers, and store at a temperature not exceeding 30°.
- RLD: Store between 2° to 30°C (36° and 86°F). Shake gently before use.
- ANDA: Store at 20° to 25°C (68° and 77°F) [See USP Controlled Room Temperature]. Shake gently before use.

6. **PACKAGING CONFIGURATIONS**

- RLD: Packages its product in amber glass bottle fitted with a white metering atomizing pump, white nasal adapter, and green dust cover in a box of 1.
- ANDA: Fluticasone Propionate Nasal Spray, 50 mcg will be contained in a 15 mL amber type I glass aerosol bottle with a metering nasal spray pump, white plastic actuator and a translucent cap.

7. **CONTAINER/CLOSURE -**

Bottle: 15 mL Amber Type I Glass Aerosol Bottle: (b) (4) (Mold # (b) (4))

Pump: (b) (4) Metering Nasal Pump with (b) (4)

Actuator/Cap: White Plastic Actuator (b) (4) and Translucent Cap (b) (4)

8. **FINISHED DOSAGE FORM**

- RLD: Spray: 50 mcg per spray
- ANDA: Milky white suspension; 50 mcg per spray

9. **MANUFACTURING FACILITY OF FINISHED DOSAGE FORM**

Apotex Inc.
380 Elgin Mills Road East
Richmond Hill, Ontario
Canada L4C 5H2

Date of Review: **Date of Submission: February 28, 2005**

Primary Reviewer: Beverly Weitzman **Date:** 7/26/2005

B. Weitzman

Team Leader: John Grace **Date:** 7/20/05

John J Grace

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cc:

ANDA: 77-538
DUP/DIVISION FILE
HFD-613/BWeitzman/JGrace (no cc)
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Review

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 77-538
Date of Submission: **November 8, 2005**
Applicant's Name: Apotex, Inc.
Established Name: Fluticasone Propionate Nasal Spray, 50 mcg

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have Final Printed Labels and Labeling? YES

1. **CONTAINER [50 mcg]** – Satisfactory in FPL as of **November 8, 2005** electronic submission.
\\Cdsesub1\evsprod\n077538\0003\m1\us\114-labeling\final-labeling\final-carton-container-labels\final-bottle-label.pdf
2. **CARTON [50 mcg]** – Satisfactory in FPL as of **November 8, 2005** electronic submission.
\\Cdsesub1\evsprod\n077538\0003\m1\us\114-labeling\final-labeling\final-carton-container-labels\final-carton.pdf
3. **PACKAGE INSERT** - Satisfactory in FPL as **November 8, 2005** of electronic submission.
\\Cdsesub1\evsprod\n077538\0003\m1\us\114-labeling\final-labeling\final-package-insert-package-inserts\final-insert.pdf

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: Flonase Nasal Spray
- NDA Number: 20-121
- NDA Drug Name: Fluticasone propionate Nasal Spray, 50 mcg
- NDA Firm: Glaxo Wellcome Inc.
- Date of Approval of NDA Insert and supplement: NDA 20-121/S-030: Approved on March 26, 2004.
- Has this been verified by the MIS system for the NDA? Yes
- Was this approval based upon an OGD labeling guidance? No
- Basis of Approval for the Container Labels: Side-by-side comparison
- Basis of Approval for the Carton Labels: Side-by-side comparison
- Revisions needed post-approval: No
- Patents/Exclusivities: Refer to chart below.

Patent Data – NDA 20-121

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
			There is no unexpired patent for this product.	II	

Exclusivity Data– NDA 20-121

Code	Reference	Expiration	Labeling Impact
PED	PEDIATRIC EXCLUSIVITY	**NOV 01,2006**	NONE
D-76	FOR USE ON AN "AS NEEDED" OR PRN BASIS FOR THE MANAGEMENT OF NASAL SYMPTOMS IN PATIENTS FOR WHOM THE DRUG IS INDICATED	**MAY 23,2005**	NONE
PED	PEDIATRIC EXCLUSIVITY	**NOV 23,2005**	NONE
M-24	INFORMATION ON RESULTS OF A LONG TERM LONGITUDINAL GROWTH STUDY AND PEDIATRIC SAFETY INFORMATION	**MAY 01,2006**	NONE

Apotex, Inc. certifies that the Aptoex Inc. product,Fluticasone Propionate Nasal Spray, 50 mcg, will not be marketed until after the expiration of the listed exclusivities and corresponding pediatric extensions.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		x	
Is this name different than that used in the Orange Book?			x
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			x
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			

Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section? [not scored]			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?			x
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		x	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		x	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		x	

NOTES/QUESTIONS TO THE CHEMIST: NONE

FOR THE RECORD:

1. **MODEL LABELING** – The review was base on Flonase Nasal Spray, 50 mcg per spray, (NDA 20-121/S-030) approved on March 26, 2004. This supplement provides for the addition of a description of fluticasone propionate's interactions with ritonavir to the CLINICAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS sections of the package insert and to the Patient's Instructions for use leaflet.

2. This drug product is **not** the subject of a USP monograph.

3. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition section.

Strength (Label Claim):		50 mcg			
Component and Quality Standard (and Grade, if applicable)	Function of Component	Theoretical Quantity			
		Per Spray (mcg/100 mg)	Per Unit (g/16 g Bottle)	Concentration (g/kg)	%
Fluticasone	Active drug	50	(b) (4)		

Propionate BP	substance				
Benzalkonium Chloride (b) (4) NF/EP ((b) (4)	(b) (4)				
Dextrose (b) (4) USP					
Microcrystalline Cellulose and Carboxymethyl-cellulose Sodium NF					
Phenylethyl Alcohol USP					
Polysorbate 80 NF (b) (4)					
Purified Water USP/EP					
TOTAL:		100 mg	16 g	1.0 kg	100.0%

4. PATENTS/EXCLUSIVITIES:

Patent Data – NDA 20-121

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
			There is no unexpired patent for this product.	II	

Exclusivity Data– NDA 20-121

Code	Reference	Expiration	Labeling Impact
PED	PEDIATRIC EXCLUSIVITY	**NOV 01,2006**	NONE
D-76	FOR USE ON AN "AS NEEDED" OR PRN BASIS FOR THE MANAGEMENT OF NASAL SYMPTOMS IN PATIENTS FOR WHOM THE DRUG IS INDICATED	**MAY 23,2005**	NONE
PED	PEDIATRIC EXCLUSIVITY	**NOV 23,2005**	NONE
M-24	INFORMATION ON RESULTS OF A LONG TERM LONGITUDINAL GROWTH STUDY AND PEDIATRIC SAFETY INFORMATION	**MAY 01,2006**	NONE

Apotex, Inc. certifies that the Aptoex Inc. product,Fluticasone Propionate Nasal Spray, 50 mcg, will not be marketed until after the expiration of the listed exclusivities and corresponding pediatric extensions.

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

- USP: Preserve in tight, light-resistant containers, and store at a temperature not exceeding 30°.
- RLD: Store between 2° to 30°C (36° and 86°F). Shake gently before use.
- ANDA: Store at 20° to 25°C (68° and 77°F) [See USP Controlled Room Temperature]. Shake gently before use.

6. PACKAGING CONFIGURATIONS

- RLD: Packages its product in amber glass bottle fitted with a white metering atomizing pump, white nasal adapter, and green dust cover in a box of 1.
- ANDA: Fluticasone Propionate Nasal Spray, 50 mcg will be contained in a 15 mL amber type I glass aerosol bottle with a metering nasal spray pump, white plastic actuator and a translucent cap.

7. **CONTAINER/CLOSURE -**

Bottle: 15 mL Amber Type I Glass Aerosol Bottle: (b) (4) (Mold # (b) (4))

Pump: (b) (4) Metering Nasal Pump with (b) (4)

Actuator/Cap: White Plastic Actuator (b) (4) and Translucent Cap (b) (4)

8. **FINISHED DOSAGE FORM**

- RLD: Spray: 50 mcg per spray
- ANDA: Milky white suspension; 50 mcg per spray

9. **MANUFACTURING FACILITY OF FINISHED DOSAGE FORM**

Apotex Inc.
380 Elgin Mills Road East
Richmond Hill, Ontario
Canada L4C 5H2

Date of Review: **Date of Submission: November 8, 2005**

Primary Reviewer: Beverly Weitzman **Date:** 12/12/2005

B. Weitzman

Team Leader: John Grace **Date:** 12/15/05

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ANDA: 77-538
DUP/DIVISION FILE
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Review

REVIEW OF PROFESSIONAL LABELING #2
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 77-538

Date of Submission: April 25, 2006 and May 26, 2006 (Gratuitous amendments)

Applicant's Name: Apotex, Inc.

Established Name: Fluticasone Propionate Nasal Spray, 50 mcg

Labeling Deficiencies:

1. **CONTAINER** (50 mcg) – Satisfactory in Final Print.
2. **CARTON** *(50 mcg)* - Satisfactory in Final Print.
3. **PATIENT INSTRUCTION** – Satisfactory in DRAFT
4. **INSERT:**

   DESCRIPTION – Revise "(b) (4)" to read "and the molecular formula"

   PRECAUTIONS- *Pediatric Use:* In the first sentence revise "Six hundred fifty (650) patients…" to read "Five hundred (500) patients…"

Please revise your insert labeling as described above and submit in final print.

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format. For additional information, please refer to 21 CFR 314.94(d)(ii), SPL Implementation Guide for FDA Content of Labeling Submissions at http://www.fda.gov/cder/regulatory/ersr/SPL2aIG_v20051006_r1.pdf and Docket 92S-0251, Memorandum 32.

Although Docket 92S-0251, Memorandum 32 states that as of October 31, 2005, Structured Product Labeling (SPL) in XML format is the only acceptable format for the submission of the content of labeling in electronic format, abbreviated new drug applications not listed as the referenced listed drug (RLD) may be submitted in PDF and MS Word until the SPL for the RLD is posted on the DailyMed website at http://dailymed.nlm.nih.gov/dailymed/about.cfm. Should you decide to take the option of waiting until the SPL for the RLD is posted on the website, you will be responsible for submitting your content of labeling in SPL within 30 days after the SPL for the RLD is posted on the DailyMed website. If you have any questions on SPL submissions, please call Mr. Koung Lee at 301-827-7336.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference-listed drug. In order to keep your ANDA current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://www.fda.gov/cder/cdernew/listserv.html or
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		x	
Is this name different than that used in the Orange Book?			x
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			x
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			x

Has the firm failed to describe the scoring in the HOW SUPPLIED section? [not scored]			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?			x
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		x	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		x	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		x	

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. **MODEL LABELING** – The review was base on Flonase Nasal Spray, 50 mcg per spray, (NDA 20-121/S-030) approved on March 26, 2004. This supplement provides for the addition of a description of fluticasone propionate's interactions with ritonavir to the CLINICAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS sections of the package insert and to the Patient's Instructions for use leaflet. Also, this drug product is **not** the subject of a USP monograph.

   Please note that the reference listed drug, Flonase Nasal Spray, received 3 years Waxman-Hatch marketing exclusivity **M-24** "INFORMATION ON RESULTS OF A LONG TERM LONGITUDINAL GROWTH STUDY AND PEDIATRIC SAFETY INFORMATION" which expires November 1, 2006. The carve out portions and text replacing all protected pediatric information was approved by the agency September 3, 2004, including concurrence from Division of Pediatric Drug Development, Division of Pulmonary and Allergy Drug Products and Office of Chief Counsel. The consult was done per Angela Payne. **See Table below** for final agreement for text replacing all protected pediatric information.

Column text changes are in bold print OR highlighted in each column	**Previously approved SE2/023, Approved 5/23/02** **Entire Pediatric subsection displayed here.**	**Fluticasone [NDA 20-121/SE8-028] Approved 1-May-2003 granted 3 years W/H exclusivity for M-24** (INFORMATION ON RESULTS OF A LONG TERM LONGITUDINAL GROWTH STUDY AND PEDIATRIC SAFETY INFORMATION)	**DPADP, DPDD, OGD, and OGC** **Agreement reached on Sept. 3, 2004**
PRECAUTIONS, Pediatric Use 1. Changed. 2. No changes. 3. New Text	1.Five hundred **(500)** patients aged 4 to 11 years and 440 patients aged 12 to 17 years were studied in US clinical trials with Fluticasone propionate nasal spray. The safety and effectiveness of FLONASE Nasal Spray in children below 4 years of age have not been established. 2. Controlled clinical studies have shown that intranasal corticosteroids... FLONASE Nasal Spray, each patient should be titrated to the lowest dose that effectively controls his/her symptoms.	1.Six hundred fifty **(650)** patients aged 4 to 11 years and 440 patients aged 12 to 17 years were studied in US clinical trials with fluticasone propionate nasal spray. The safety and effectiveness of FLONASE Nasal Spray in children below 4 years of age have not been established. 2. No Change. **3. A 1-year placebo-controlled clinical growth study was conducted in 150 pediatric patients (ages 3 to 9 years) to assess the effect of FLONASE Nasal Spray (single daily dose of 200 mcg, the maximum approved dose) on growth velocity. From the primary population of 56 patients receiving FLONASE Nasal Spray subjects and 52 receiving placebo subjects, the point estimate for growth velocity with FLONASE Nasal Spray was 0.14 cm/year lower than that noted**	1. Five hundred **(500)** patients aged 4 to 11 years and 440 patients aged 12 to 17 years were studied in US clinical trials with fluticasone propionate nasal spray. The safety and effectiveness of Fluticasone Nasal Spray in children below 4 years of age have not been established. 2.No Change. **3. Pediatric Use INFORMATION ON RESULTS OF A LONG TERM LONGITUDINAL GROWTH STUDY for Fluticasone is approved for GlaxoSmithKline's Fluticasone Propionate Nasal Spray. However, due to GalxoSmithKline' s marketing exclusivity rights, this drug product is not labeled with that pediatric information.**

4. New text.		**with placebo (95% confidence interval ranging from 0.54 cm/year lower than placebo to 0.27 cm/year higher than placebo). Thus, no statistically significant effect on growth was noted compared to placebo. No evidence of clinically relevant changes in HPA axis function or bone mineral density was observed as assessed by 12-hour urinary cortisol excretion and dual-energy x-ray absorptiometry, respectively.** **4.The potential for FLONASE Nasal Spray to cause growth suppression in susceptible patients or when given at higher doses cannot be ruled out.**	**4. Delete Paragraph #4. It will be covered under disclaimer used in paragraph #3**

2. LABELING ISSUES:

a. **EXCLUSIVITY:** Please note that the exclusivity statement **has been revised** to indicate that Apotex Inc. product will not infringe upon GlaxoSmithKlines marketing exclusivity rights. Apotex submitted a gratuitous labeling April 25, 2006 and May 26, 2006 to revise their labeling to carve out Peds exclusivity M-24 "INFORMATION ON RESULTS OF A LONG TERM LONGITUDINAL GROWTH STUDY AND PEDIATRIC SAFETY INFORMATION" **Therefore this review supercedes the Approval Summary from November 8, 2005.**

b. **LABELING:**

- **CONTAINER [50 mcg]** – Satisfactory in FPL as of **November 8, 2005** electronic submission. **\\Cdsesub1\evsprod\n077538\0003\m1\us\114-labeling\final-labeling\final-carton-container-labels\final-bottle-label.pdf**

- **CARTON [50 mcg]** – Satisfactory in FPL as of **November 8, 2005** electronic submission. **\\Cdsesub1\evsprod\n077538\0003\m1\us\114-labeling\final-labeling\final-carton-container-labels\final-carton.pdf**
- **PACKAGE INSERT** – NOT Satisfactory in FPL as of May 26, 2006 electronic submission.

3. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition section.

Strength (Label Claim):		50 mcg			
Component and Quality Standard (and Grade, if applicable)	Function of Component	Theoretical Quantity			
		Per Spray (mcg/100 mg)	Per Unit (g/16 g Bottle)	Concentration (g/kg)	%
Fluticasone Propionate BP	Active drug substance	50	(b) (4)		
Benzalkonium Chloride (b) (4) NF/EP ((b))					
Dextrose (b) (4) USP					
Microcrystalline Cellulose and Carboxymethyl-cellulose Sodium NF					
Phenylethyl Alcohol USP					
Polysorbate 80 NF (b) (4)					
Purified Water USP/EP					
TOTAL:		100 mg	16 g	1.0 kg	100.0%

(b) (4)

4. **PATENTS/EXCLUSIVITIES:**

Patent Data – NDA 20-121

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
			There is no unexpired patent for this product.	II	

Exclusivity Data– NDA 20-121

Code	Reference	Expiration	Labeling Impact
M-24/S-028	**INFORMATION ON RESULTS OF A LONG TERM LONGITUDINAL GROWTH STUDY AND PEDIATRIC SAFETY INFORMATION**	**May 01, 2006 peds, Nov. 1, 2006**	***BPCA used per consult. (Precaution, Pediatric subsection, final paragraph)***
D-76/S-023	FOR USE ON AN "AS NEEDED" OR PRN BASIS FOR THE MANAGEMENT OF NASAL SYMPTOMS IN PATIENTS FOR WHOM THE DRUG IS INDICATED	*May 23, 2005* Ped Nov. 23, 2005	NONE - EXPIRED

5. **STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON**

- USP: Preserve in tight, light-resistant containers, and store at a temperature not exceeding 30°.
- RLD: Store between 2° to 30°C (36° and 86°F). Shake gently before use.
- ANDA: Store at 20° to 25°C (68° and 77°F) [See USP Controlled Room Temperature]. Shake gently before use.

6. **PACKAGING CONFIGURATIONS**

- RLD: Packages its product in amber glass bottle fitted with a white metering atomizing pump, white nasal adapter, and green dust cover in a box of 1.
- ANDA: Fluticasone Propionate Nasal Spray, 50 mcg will be contained in a 15 mL amber type I glass aerosol bottle with a metering nasal spray pump, white plastic actuator and a translucent cap.

7. **CONTAINER/CLOSURE -**

Bottle: 15 mL Amber Type I Glass Aerosol Bottle: (b) (4) (Mold # (b) (4))

Pump: (b) (4) Metering Nasal Pump with (b) (4) Gasket: (b) (4)

Actuator/Cap: White Plastic Actuator (b) (4) and Translucent Cap (b) (4)

8. **FINISHED DOSAGE FORM**

- RLD: Spray: 50 mcg per spray
- ANDA: Milky white suspension; 50 mcg per spray

9. **MANUFACTURING FACILITY OF FINISHED DOSAGE FORM**

Apotex Inc.
380 Elgin Mills Road East
Richmond Hill, Ontario
Canada L4C 5H2

Date of Review: **Date of Submission:** April 25, 2006 and May 26, 2006

Primary Reviewer: Beverly Weitzman **Date:** 6/

Team Leader: John Grace **Date:** 6-15-06

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cc:

ANDA: 77-538
DUP/DIVISION FILE
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Review

APPROVAL SUMMARY #2

Supercedes Approval Summary #1 from November 8, 2005 submission

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 77-538

Date of Submission: **June 23, 2006**

Applicant's Name: Apotex, Inc.

Established Name: Fluticasone Propionate Nasal Spray, 50 mcg

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have Final Printed Labels and Labeling? YES

CONTAINER [50 mcg] – Satisfactory in FPL as of **November 8, 2005** electronic submission.
\\Cdsesub1\evsprod\n077538\0003\m1\us\114-labeling\final-labeling\final-carton-container-labels\final-bottle-label.pdf

CARTON [50 mcg] – Satisfactory in FPL as of **November 8, 2005** electronic submission.
\\Cdsesub1\evsprod\n077538\0003\m1\us\114-labeling\final-labeling\final-carton-container-labels\final-carton.pdf

PACKAGE INSERT – Satisfactory in FPL as of June 23, 2006 electronic submission.
\\CDSESUB1\evsprod\n077538\0014\m1\us\114-labeling\final-labeling\final-package-insert-package-inserts\final-insert-pdf.pdf

PATIENT INFORMATION - Satisfactory in FPL as of June 23, 2006 electronic submission.
\\CDSESUB1\evsprod\n077538\0014\m1\us\114-labeling\final-labeling\final-package-insert-package-inserts\final-insert-pdf.pdf

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: Flonase Nasal Spray
- NDA Number: 20-121
- NDA Drug Name: Fluticasone propionate Nasal Spray, 50 mcg
- NDA Firm: Glaxo Wellcome Inc.
- Date of Approval of NDA Insert and supplement: NDA 20-121/S-030: Approved on March 26, 2004.
- Has this been verified by the MIS system for the NDA? Yes
- Was this approval based upon an OGD labeling guidance? No
- Basis of Approval for the Container Labels: Side-by-side comparison
- Basis of Approval for the Carton Labels: Side-by-side comparison
- Revisions needed post-approval: No
- Patents/Exclusivities: Refer to chart below.

Patent Data – NDA 20-121

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
			There is no unexpired patent for this product.	II	

Exclusivity Data– NDA 20-121

Code	Reference	Expiration	Labeling Impact
M-24/S-028	INFORMATION ON RESULTS OF A LONG TERM LONGITUDINAL GROWTH STUDY AND PEDIATRIC SAFETY INFORMATION	May 01, 2006 peds, Nov. 1, 2006	*BPCA used per consult. (Precaution, Pediatric subsection, final paragraph)*

D-76/S-023	FOR USE ON AN "AS NEEDED" OR PRN BASIS FOR THE MANAGEMENT OF NASAL SYMPTOMS IN PATIENTS FOR WHOM THE DRUG IS INDICATED	*May 23, 2005* Ped Nov. 23, 2005	NONE - EXPIRED

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		x	
Is this name different than that used in the Orange Book?			x
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	

Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			x
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section? [not scored]			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		x	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?			x
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		x	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		x	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		x	

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. **MODEL LABELING** – The review was base on Flonase Nasal Spray, 50 mcg per spray, (NDA 20-121/S-030) approved on March 26, 2004. This supplement provides for the addition of a description of fluticasone propionate's interactions with ritonavir to the CLINICAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS sections of the package insert and to the Patient's Instructions for use leaflet. Also, this drug product is **not** the subject of a USP monograph.

   Please note that the reference listed drug, Flonase Nasal Spray, received 3 years Waxman-Hatch marketing exclusivity **M-24** "INFORMATION ON RESULTS OF A LONG TERM LONGITUDINAL GROWTH STUDY AND PEDIATRIC SAFETY INFORMATION" which expires November 1, 2006. The carve out portions and text replacing all protected pediatric information was approved by the agency September 3, 2004, including concurrence from Division of Pediatric Drug Development, Division of Pulmonary and Allergy Drug Products and Office of Chief Counsel. The consult was done per Angela Payne. **See Table below** for final agreement for text replacing all protected pediatric information.

Column text changes are in bold print OR highlighted in each column	**Previously approved SE2/023, Approved 5/23/02** **Entire Pediatric subsection displayed here.**	**Fluticasone [NDA 20-121/SE8-028] Approved 1-May-2003 granted 3 years W/H exclusivity for M-24** (INFORMATION ON RESULTS OF A LONG TERM LONGITUDINAL GROWTH STUDY AND PEDIATRIC SAFETY INFORMATION)	**DPADP, DPDD, OGD, and OGC** **Agreement reached on Sept. 3, 2004**
PRECAUTIONS, Pediatric Use 1. Changed. 2. No changes. 3. New Text	1.Five hundred **(500)** patients aged 4 to 11 years and 440 patients aged 12 to 17 years were studied in US clinical trials with Fluticasone propionate nasal spray. The safety and effectiveness of FLONASE Nasal Spray in children below 4 years of age have not been established. 2. Controlled clinical studies have shown that intranasal corticosteroids... FLONASE Nasal Spray, each patient should be titrated to the lowest dose that effectively controls his/her symptoms.	1.Six hundred fifty **(650)** patients aged 4 to 11 years and 440 patients aged 12 to 17 years were studied in US clinical trials with fluticasone propionate nasal spray. The safety and effectiveness of FLONASE Nasal Spray in children below 4 years of age have not been established. 2. No Change. **3. A 1-year placebo-controlled clinical growth study was conducted in 150 pediatric patients (ages 3 to 9 years) to assess the effect of FLONASE Nasal Spray (single daily dose of 200 mcg, the maximum approved dose) on growth velocity. From the primary population of 56 patients receiving FLONASE Nasal Spray subjects and 52 receiving placebo subjects, the point estimate for growth velocity with FLONASE Nasal Spray was 0.14 cm/year lower than that noted**	1. Five hundred **(500)** patients aged 4 to 11 years and 440 patients aged 12 to 17 years were studied in US clinical trials with fluticasone propionate nasal spray. The safety and effectiveness of Fluticasone Nasal Spray in children below 4 years of age have not been established. 2.No Change. **3. Pediatric Use INFORMATION ON RESULTS OF A LONG TERM LONGITUDINAL GROWTH STUDY for Fluticasone is approved for GlaxoSmithKline's Fluticasone Propionate Nasal Spray. However, due to GalxoSmithKline' s marketing exclusivity rights, this drug product is not labeled with that pediatric information.**

4. New text.		**with placebo (95% confidence interval ranging from 0.54 cm/year lower than placebo to 0.27 cm/year higher than placebo). Thus, no statistically significant effect on growth was noted compared to placebo. No evidence of clinically relevant changes in HPA axis function or bone mineral density was observed as assessed by 12-hour urinary cortisol excretion and dual-energy x-ray absorptiometry, respectively.** **4.The potential for FLONASE Nasal Spray to cause growth suppression in susceptible patients or when given at higher doses cannot be ruled out.**	**4. Delete Paragraph #4. It will be covered under disclaimer used in paragraph #3**

2. LABELING ISSUES:

a. **EXCLUSIVITY:** Please note that the exclusivity statement **has been revised** to indicate that Apotex Inc. product will not infringe upon GlaxoSmithKlines marketing exclusivity rights. Apotex submitted a gratuitous labeling April 25, 2006 and May 26, 2006 to revise their labeling to carve out Peds exclusivity M-24 "INFORMATION ON RESULTS OF A LONG TERM LONGITUDINAL GROWTH STUDY AND PEDIATRIC SAFETY INFORMATION" **Therefore this review supercedes the Approval Summary from November 8, 2005.**

b. **LABELING:**

- **CONTAINER [50 mcg]** – Satisfactory in FPL as of **November 8, 2005** electronic submission. **\\Cdsesub1\evsprod\n077538\0003\m1\us\114-labeling\final-labeling\final-carton-container-labels\final-bottle-label.pdf**
- **CARTON [50 mcg]** – Satisfactory in FPL as of **November 8, 2005** electronic submission. **\\Cdsesub1\evsprod\n077538\0003\m1\us\114-labeling\final-labeling\final-carton-container-labels\final-carton.pdf**
- **PACKAGE INSERT** – Satisfactory in FPL as of June 23, 2006 electronic submission.

3. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition section.

Strength (Label Claim):		50 mcg			
Component and Quality Standard (and Grade, if applicable)	Function of Component	Theoretical Quantity			
		Per Spray (mcg/100 mg)	Per Unit (g/16 g Bottle)	Concentration (g/kg)	%
Fluticasone Propionate BP	Active drug substance	50	(b) (4)		
Benzalkonium Chloride (b) (4) NF/EP ((b))			(b) (4)		
Dextrose (b) (4) USP					
Microcrystalline Cellulose and Carboxymethyl-cellulose Sodium NF					
Phenylethyl Alcohol USP					
Polysorbate 80 NF (b) (4)					
Purified Water USP/EP					
TOTAL:		100 mg	16 g	1.0 kg	100.0%

4. PATENTS/EXCLUSIVITIES:

Patent Data – NDA 20-121

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
			There is no unexpired patent for this product.	II	

Exclusivity Data– NDA 20-121

Code	Reference	Expiration	Labeling Impact
M-24/S-028	**INFORMATION ON RESULTS OF A LONG TERM LONGITUDINAL GROWTH STUDY AND PEDIATRIC SAFETY INFORMATION**	**May 01, 2006 peds, Nov. 1, 2006**	***BPCA used per consult. (Precaution, Pediatric subsection, final paragraph)***
D-76/S-023	FOR USE ON AN "AS NEEDED" OR PRN BASIS FOR THE MANAGEMENT OF NASAL SYMPTOMS IN PATIENTS FOR WHOM THE DRUG IS INDICATED	*May 23, 2005* Ped Nov. 23, 2005	NONE - EXPIRED

5. **STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON**

- USP: Preserve in tight, light-resistant containers, and store at a temperature not exceeding 30°.
- RLD: Store between 2° to 30°C (36° and 86°F). Shake gently before use.
- ANDA: Store at 20° to 25°C (68° and 77°F) [See USP Controlled Room Temperature]. Shake gently before use.

6. **PACKAGING CONFIGURATIONS**

- RLD: Packages its product in amber glass bottle fitted with a white metering atomizing pump, white nasal adapter, and green dust cover in a box of 1.
- ANDA: Fluticasone Propionate Nasal Spray, 50 mcg will be contained in a 15 mL amber type I glass aerosol bottle with a metering nasal spray pump, white plastic actuator and a translucent cap.

7. **CONTAINER/CLOSURE -**

Bottle: 15 mL Amber Type I Glass Aerosol Bottle (b) (4) (Mold # (b) (4))

Pump: (b) (4) Metering Nasal Pump with (b) (4) Gasket: (b) (4)

Actuator/Cap: White Plastic Actuator (b) (4) and Translucent Cap (b) (4)

8. **FINISHED DOSAGE FORM**

- RLD: Spray: 50 mcg per spray
- ANDA: Milky white suspension; 50 mcg per spray

9. **MANUFACTURING FACILITY OF FINISHED DOSAGE FORM**

Apotex Inc.
380 Elgin Mills Road East
Richmond Hill, Ontario
Canada L4C 5H2

Date of Review: **Date of Submission: June 23, 2006**

Primary Reviewer: Beverly Weitzman **Date:** 7/10/2006

Team Leader: John Grace **Date:** 7.13.06

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cc:

ANDA: 77-538
DUP/DIVISION FILE
HFD-613/BWeitzman/JGrace (no cc)
V:\FIRMSAM\Apotex\LTRS&REV\77538.AP2L.doc
Review

APPROVAL SUMMARY #3 – Effective After 11/1/2006

Supersedes Approval Summary #2 from June 23, 2006 submission

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 77-538 Date of Submission: **October 17, 2006**

Applicant's Name: Apotex, Inc.

Established Name: Fluticasone Propionate Nasal Spray, 50 mcg

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have Final Printed Labels and Labeling? YES

CONTAINER [50 mcg] – Satisfactory in FPL as of **November 8, 2005** electronic submission.
\\Cdsesub1\evsprod\n077538\0003\m1\us\114-labeling\final-labeling\final-carton-container-labels\final-bottle-label.pdf

CARTON [50 mcg] – Satisfactory in FPL as of **November 8, 2005** electronic submission.
\\Cdsesub1\evsprod\n077538\0003\m1\us\114-labeling\final-labeling\final-carton-container-labels\final-carton.pdf

PACKAGE INSERT – Satisfactory in FPL as of October 17, 2006 electronic submission.

PATIENT INFORMATION - Satisfactory in FPL as of October 17, 2006 electronic submission.

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: Flonase Nasal Spray
- NDA Number: 20-121
- NDA Drug Name: Fluticasone propionate Nasal Spray, 50 mcg
- NDA Firm: Glaxo Wellcome Inc.
- Date of Approval of NDA Insert and supplement: NDA 20-121/S-030: Approved on March 26, 2004.
- Has this been verified by the MIS system for the NDA? Yes
- Was this approval based upon an OGD labeling guidance? No
- Basis of Approval for the Container Labels: Side-by-side comparison
- Basis of Approval for the Carton Labels: Side-by-side comparison
- Revisions needed post-approval: No
- Patents/Exclusivities: Refer to chart below.

Patent Data – NDA 20-121

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
			There is no unexpired patent for this product.	II	

Exclusivity Data– NDA 20-121

Code	Reference	Expiration	Labeling Impact
M-24/S-028	**INFORMATION ON RESULTS OF A LONG TERM LONGITUDINAL GROWTH STUDY AND PEDIATRIC SAFETY INFORMATION**	**May 01, 2006 peds, Nov. 1, 2006**	**NONE – EXPIRED as of 11/1/2006**
D-76/S-023	FOR USE ON AN "AS NEEDED" OR PRN BASIS FOR THE MANAGEMENT OF NASAL SYMPTOMS IN PATIENTS FOR WHOM THE DRUG IS INDICATED	*May 23, 2005* Ped Nov. 23, 2005	NONE - EXPIRED

FOR THE RECORD:

1. **MODEL LABELING** – The review was base on Flonase Nasal Spray, 50 mcg per spray, (NDA 20-121/S-030) approved on March 26, 2004. This supplement provides for the addition of a description of fluticasone propionate's interactions with ritonavir to the CLINICAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS sections of the package insert and to the Patient's Instructions for use leaflet. Also, this drug product is **not** the subject of a USP monograph.

Please note that the reference listed drug, Flonase Nasal Spray, received 3 years Waxman-Hatch marketing exclusivity **M-24** "INFORMATION ON RESULTS OF A LONG TERM LONGITUDINAL GROWTH STUDY AND PEDIATRIC SAFETY INFORMATION" which expires November 1, 2006. The sponsor has replaced this text ahead of the 11/1/2006 date.

2. **LABELING ISSUES:**

EXCLUSIVITY: Please note that the exclusivity statement **has been revised** to indicate that Apotex Inc. product will not infringe upon GlaxoSmithKlines marketing exclusivity rights. Apotex submitted a gratuitous labeling October 17, 2006 to revise their labeling to replace information regarding the Pediatric exclusivity M-24 "INFORMATION ON RESULTS OF A LONG TERM LONGITUDINAL GROWTH STUDY AND PEDIATRIC SAFETY INFORMATION" **Therefore this review supersedes the Approval Summary from June 23, 2006.**

3. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition section.

4. **PATENTS/EXCLUSIVITIES:**

Patent Data – NDA 20-121

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
			There is no unexpired patent for this product.	II	

Exclusivity Data– NDA 20-121

Code	Reference	Expiration	Labeling Impact
M-24/S-028	**INFORMATION ON RESULTS OF A LONG TERM LONGITUDINAL GROWTH STUDY AND PEDIATRIC SAFETY INFORMATION**	**May 01, 2006 peds, Nov. 1, 2006**	***BPCA used per consult. (Precaution, Pediatric subsection, final paragraph)***
D-76/S-023	FOR USE ON AN "AS NEEDED" OR PRN BASIS FOR THE MANAGEMENT OF NASAL SYMPTOMS IN PATIENTS FOR WHOM THE DRUG IS INDICATED	*May 23, 2005* Ped Nov. 23, 2005	NONE - EXPIRED

5. **STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON**

- USP: Preserve in tight, light-resistant containers, and store at a temperature not exceeding 30°.
- RLD: Store between 2° to 30°C (36° and 86°F). Shake gently before use.
- ANDA: Store at 20° to 25°C (68° and 77°F) [See USP Controlled Room Temperature]. Shake gently before use.

6. **PACKAGING CONFIGURATIONS**

- RLD: Packages its product in amber glass bottle fitted with a white metering atomizing pump, white nasal adapter, and green dust cover in a box of 1.
- ANDA: Fluticasone Propionate Nasal Spray, 50 mcg will be contained in a 15 mL amber type I glass aerosol bottle with a metering nasal spray pump, white plastic actuator and a translucent cap.

7. **CONTAINER/CLOSURE -**

Bottle: 15 mL Amber Type I Glass Aerosol Bottle: (b) (4) (Mold # (b) (4)

Pump: (b) (4) Metering Nasal Pump with (b) (4)

Actuator/Cap: White Plastic Actuator (b) (4) and Translucent Cap (b) (4)

8. **FINISHED DOSAGE FORM**

- RLD: Spray: 50 mcg per spray
- ANDA: Milky white suspension; 50 mcg per spray

9. **MANUFACTURING FACILITY OF FINISHED DOSAGE FORM**

Apotex Inc.
380 Elgin Mills Road East
Richmond Hill, Ontario
Canada L4C 5H2

Date of Review: October 24, 2006 **Date of Submission: October 17, 2006**

Primary Reviewer: Charlie Hoppes **Date:**

Team Leader: John Grace **Date:**

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Charles Hoppes
10/25/2006 09:05:02 AM
MEDICAL OFFICER

John Grace
10/25/2006 02:35:47 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-538

CHEMISTRY REVIEWS

#1

CHEMISTRY REVIEW

ANDA 77-538

Fluticasone Propionate Nasal Spray, 50 ug/Spray

Apotex Inc.

Kenneth J. Furnkranz
Division of Chemistry 1

Chemistry Review #1

Table of Contents

Chemistry Review Data Sheet

1. ANDA 77-538

2. REVIEW #: 1

3. REVIEW DATE: October 24, 2005

4. REVIEWER: Kenneth J. Furnkranz

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original ANDA submission	February 28, 2005

7. NAME & ADDRESS OF APPLICANT:

Name:	Apotex Inc.
Address:	380 Elgin Mills Road East Richmond Hills Ontario, Canada L4C 5H2
U.S. Agent	Apotex Corp. Kalpesh Shroff 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326
ANDA Contact	Marcy McDonald
Telephone:	(954)-349-4217

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Fluticasone Propionate

9. LEGAL BASIS FOR SUBMISSION:

Chemistry Review Data Sheet

The RLD for this ANDA is Flonase® (Fluticasone Propionate) Nasal Spray 50 mcg; GlaxoSmithKline (NDA 20-121). Apotex has provided Patent and Exclusivity information and a printout of the Orange Book listing showing no unexpired patents and current exclusivities.

10. PHARMACOLOGICAL CATEGORY:

Management of nasal symptoms of seasonal and perennial allergic and nonallergic rhinitis in adults and pediatric patients 4 years of age and older.

11. DOSAGE FORM: Spray, Metered, Nasal CODE: 836

12. STRENGTH/POTENCY: 50 µg/Spray

13. ROUTE OF ADMINISTRATION: Nasal CODE: 014

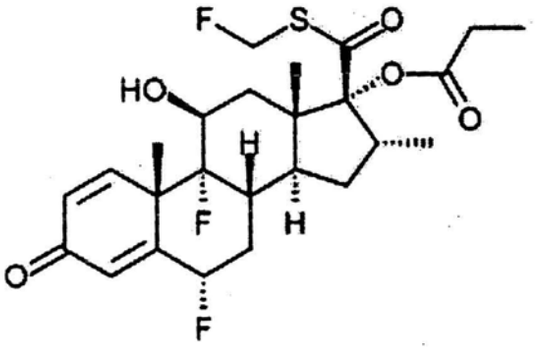
14. Rx/OTC DISPENSED: __X__Rx ____OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



S-(fluoromethyl)6α,9-difluoro-11β-17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate

Molecular Weight: 500.6
Empirical Formula: $C_{25}H_{31}F_3O_5S$

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Inadequate	10/19/05	-
	III			4	-	-	-
	III			4	-	-	-
	III			4	-	-	-
	III			4	-	-	-

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	To be performed later		
Labeling	Deficient	8/25/05	B. Weitzman
Bioequivalence	Pending Review		
EA	Acceptable	10/24/05	K.Furnkranz
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

Chemistry Review Data Sheet

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for A/NDA 77-538

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable - MINOR Amendment

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None identified at this time

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The active ingredient in the drug product is Fluticasone Propionate. The drug substance is a white to off-white powder.

The drug product is an aqueous suspension containing microfine fluticasone propionate and other inactive ingredients, including (b) (4) Each container delivers at least 120 sprays. The drug product is filled into amber vials which are capped with a metered spray pump, actuator and dust cap. The drug product is for topical administration to the nasal mucosa by means of a metering, atomizing spray pump.

B. Description of How the Drug Product is Intended to be Used

Fluticasone Propionate Nasal Spray is used in the management of nasal symptoms of seasonal and perennial allergic and nonallergic rhinitis in adults and children. The drug product is administered by a metered spray pump which delivers 50 mcg/spray. The Dosage and Administration section of the package insert labeling indicates that the usual adult dosage is 200 mcg/day given either once (2 sprays in each nostril once daily) or twice (1 spray in each nostril twice daily). The Maximum Daily Dose (MDD) is 200 mcg.

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is Not Approvable due to MINOR deficiencies with the drug substance and drug product specifications, manufacturing instructions, in-process, finished product and stability controls and other deficiencies.

The drug product is a nasal suspension with the critical attributes being the particle size distribution of the drug in the spray, particle size distribution of the suspending agents, droplet size distribution of the spray and the spray pattern of the device. These attributes may affect the delivered dose. These characteristics may also be impacted by the pump and actuator geometry.

III. Administrative

A. Reviewer's Signature Kenneth J. Furnkranz

DATE COMPLETED: 10/24/05
DATE REVISED:

B. Endorsement Block

HFD-625/K.Furnkranz, Review Chemist 11/3/05
HFD-625/M.Smela, Team Leader

C. CC Block

ANDA 77-538
ANDA DUP
DIV FILE
Field Copy

Following this page, 43 pages are withheld in full (b)(4).
Chemistry Review #1.

6. An acceptable compliance evaluation is needed for approval. We have requested an evaluation from the Office of Compliance.

Sincerely yours,

M Smela for 11/4/05

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 77-538
ANDA DUP
DIV FILE
Field Copy

Endorsements:
HFD-625/K.Furnkranz, Review Chemist 11/4/05
HFD-625/M.Smela, Team Leader/11/1/05 11/4/05
HFD-617/P.Chen, Project Manager/11/1/05 11/3/05
F/T by:ard/11/2/05
V:\FIRMSAM\Apotex\LTRS&REV\77538Rev01kjf.doc
TYPE OF LETTER: Not Approvable MINOR Amendment

#2

CHEMISTRY REVIEW

ANDA 77-538

Fluticasone Propionate Nasal Spray, 50 ug/Spray

Apotex Inc.

Kenneth J. Furnkranz
Division of Chemistry 1

Chemistry Review #2

Table of Contents

Chemistry Review Data Sheet

1. ANDA 77-538

2. REVIEW #: 2

3. REVIEW DATE: February 6, 2006

4. REVIEWER: Kenneth J. Furnkranz

5. PREVIOUS DOCUMENTS: None

Submission(s) Reviewed	Document Date
Original ANDA submission	February 28, 2005
Bioequivalence Amendment	May 26. 2005
Bioequivalence Amendment	August 12, 2005
New Correspondence (agent)	August 30, 2005
Labeling Amendment	November 8, 2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
*MINOR Amendment	January 11, 2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Apotex Inc.
Address:	380 Elgin Mills Road East Richmond Hills Ontario, Canada L4C 5H2
U.S. Agent	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326
ANDA Contact	Tammy McIntire
Telephone:	(905-884-2050

Executive Summary Section

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Fluticasone Propionate

9. LEGAL BASIS FOR SUBMISSION:

The RLD for this ANDA is Flonase® (Fluticasone Propionate) Nasal Spray 50 mcg; GlaxoSmithKline (NDA 20-121). Apotex has provided Patent and Exclusivity information and a printout of the Orange Book listing showing no unexpired patents and current exclusivities.

10. PHARMACOLOGICAL CATEGORY:

Management of nasal symptoms of seasonal and perennial allergic and nonallergic rhinitis in adults and pediatric patients 4 years of age and older.

11. DOSAGE FORM: Spray, Metered, Nasal CODE: 836

12. STRENGTH/POTENCY: 50 µg/Spray

13. ROUTE OF ADMINISTRATION: Nasal CODE: 014

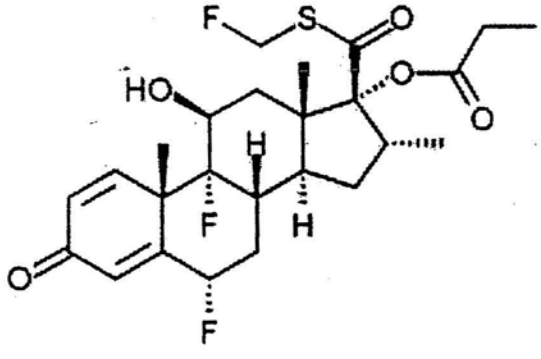
14. Rx/OTC DISPENSED: __X__Rx ____OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Executive Summary Section

S-(fluoromethyl)6α,9-difluoro-11β-17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate

Molecular Weight: 500.6
Empirical Formula: $C_{25}H_{31}F_3O_5S$

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Deficient*	2/8/06	-
	III			4	-	-	-
	III			4	-	-	-
	III			4	-	-	-
	III			4	-	-	-

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

* - Although the DMF is deemed deficient, the deficiencies are related to the specifications for (b) (4) Apotex has addressed these discrepancies in their ANDA submission and their specifications for Fluticasone Propionate received by them are in conformance with the monograph.

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC	RECOMMENDATION	DATE	REVIEWER

Executive Summary Section

RELATED REVIEWS			
Microbiology	N/A		
EES	Pending		
Methods Validation	Not Ready		
Labeling	Satisfactory	12/15/05	B.Weitzman/J.Grace
Bioequivalence	Pending Review		
EA	Acceptable	10/24/05	K.Furnkranz
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes __X__ No If no, explain reason(s) below:

MINOR Amendment submission.

The Chemistry Review for ANDA 77-538

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable - MINOR Amendment

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None identified at this time

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The active ingredient in the drug product is Fluticasone Propionate. The drug substance is a white to off-white powder.

The drug product is an aqueous suspension containing microfine fluticasone propionate and other inactive ingredients, including (b) (4) . Each container delivers at least 120 sprays. The drug product is filled into amber vials which are capped with a metered spray pump, actuator and dust cap. The drug product is for topical administration to the nasal mucosa by means of a metering, atomizing spray pump.

B. Description of How the Drug Product is Intended to be Used

Fluticasone Propionate Nasal Spray is used in the management of nasal symptoms of seasonal and perennial allergic and nonallergic rhinitis in adults and children. The drug product is administered by a metered spray pump which delivers 50 mcg/spray. The Dosage and Administration section of the package insert labeling indicates that the usual adult dosage is 200 mcg/day given either once (2 sprays in each nostril once daily) or twice (1 spray in each nostril twice daily). The Maximum Daily Dose (MDD) is 200 mcg.

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is Not Approvable due to MINOR deficiencies.

Following this page, 30 pages are withheld in full.
Chemistry Review #2.

Executive Summary Section

The drug product is a nasal suspension with the critical attributes being the particle size distribution of the drug in the spray, particle size distribution of the suspending agents, droplet size distribution of the spray and the spray pattern of the device. These attributes may affect the delivered dose. These characteristics may also be impacted by the pump and actuator geometry.

III. Administrative

A. Reviewer's Signature Kenneth J. Furnkranz

DATE COMPLETED: 2/6/06
DATE REVISED:

B. Endorsement Block 2/15/06

HFD-625/K.Furnkranz, Review Chemist/2/9/06
HFD-625/M.Smela, Team Leader/**2/10/06**

C. CC Block

ANDA 77-538
ANDA DUP
DIV FILE
Field Copy
Not Approvable MINOR Amendment

4. We note and acknowledge your commitments regarding the establishment of DSD and Spray Pattern specifications post-approval. However, with regard to sample requirements, we request that you provide data from 5 units from each of the first 20 batches, as we would like to standardize the data collection and evaluation for all generic applicants of this drug product. As a result, we request that you comply with our request as previously stated and provide data from 5 units per batch.

Sincerely yours,

M. Smela for 2/16/06

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

cc: ANDA 77-538
ANDA DUP
DIV FILE
Field Copy

Endorsements:
HFD-625/K.Furnkranz, Review Chemist/2/9/06 2/15/06
HFD-625/M.Smela, Team Leader/2/10/06 2/16/06
HFD-617/P.Chen, Project Manager/2/10/06 2/16/06
F/T by:ard/2/13/06
V:\FIRMSAM\Apotex\LTRS&REV\77538Rev02kjf.doc
TYPE OF LETTER: Not Approvable MINOR Amendment

#3

CDER CHEMISTRY REVIEW CDER

ANDA 77-538

Fluticasone Propionate Nasal Spray, 50 ug/Spray

Apotex Inc.

Kenneth J. Furnkranz
Division of Chemistry 1

Table of Contents

Chemistry Review Data Sheet

1. ANDA 77-538

2. REVIEW #: 3

3. REVIEW DATE: April 5, 2006

4. REVIEWER: Kenneth J. Furnkranz

5. PREVIOUS DOCUMENTS: None

Submission(s) Reviewed	Document Date
Original ANDA submission	February 28, 2005
Bioequivalence Amendment	May 26. 2005
Bioequivalence Amendment	August 12, 2005
New Correspondence (agent)	August 30, 2005
Labeling Amendment	November 8, 2005
MINOR Amendment	January 11, 2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
*MINOR Amendment	March 22, 2006
*Gratuitous Amendment	April 5, 2006
Bio Amendment	April 20, 2006
Labeling Amendment	April 26, 2006
*Telephone Amendment	April 28, 2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Apotex Inc.
Address:	380 Elgin Mills Road East Richmond Hills Ontario, Canada L4C 5H2
U.S. Agent	Apotex Corp. 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326

CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

ANDA Contact: Paul Bonnici

Telephone: (905-884-2050

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Fluticasone Propionate

9. LEGAL BASIS FOR SUBMISSION:

The RLD for this ANDA is Flonase® (Fluticasone Propionate) Nasal Spray 50 mcg; GlaxoSmithKline (NDA 20-121). Apotex has provided Patent and Exclusivity information and a printout of the Orange Book listing showing no unexpired patents and current exclusivities.

10. PHARMACOLOGICAL CATEGORY:

Management of nasal symptoms of seasonal and perennial allergic and nonallergic rhinitis in adults and pediatric patients 4 years of age and older.

11. DOSAGE FORM: Spray, Metered, Nasal CODE: 836

12. STRENGTH/POTENCY: 50 µg/Spray

13. ROUTE OF ADMINISTRATION: Nasal CODE: 014

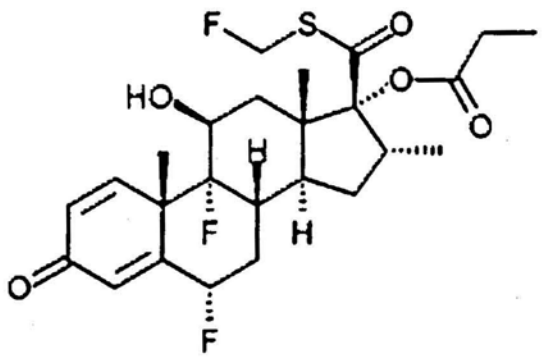
14. Rx/OTC DISPENSED: __X__Rx ____OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



S-(fluoromethyl)6α,9-difluoro-11β-17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate

Molecular Weight: 500.6
Empirical Formula: $C_{25}H_{31}F_3O_5S$

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	4/5/06	-
	III			4	-	-	-
	III			4	-	-	-
	III			4	-	-	-
	III			4	-	-	-

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
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4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	**Pending**		
Methods Validation	**Pending**		
Labeling	**Pending**		B.Weitzman/J.Grace
Bioequivalence	**Pending**		
EA	Acceptable	10/24/05	K.Furnkranz
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes __X__ No If no, explain reason(s) below:

MINOR Amendment submission.

The Chemistry Review for ANDA 77-538

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability: Approvable for CMC

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: DSD/SP commitment for finalization has been made.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The active ingredient in the drug product is Fluticasone Propionate. The drug substance is a white to off-white powder.

The drug product is an aqueous suspension containing microfine fluticasone propionate and other inactive ingredients, including (b) (4) Each container delivers at least 120 sprays. The drug product is filled into amber vials which are capped with a metered spray pump, actuator and dust cap. The drug product is for topical administration to the nasal mucosa by means of a metering, atomizing spray pump.

B. Description of How the Drug Product is Intended to be Used

The drug product is used in the management of nasal symptoms of seasonal and perennial allergic and nonallergic rhinitis in adults and children. The drug product is administered by a metered spray pump which delivers 50 mcg/spray. The Dosage and Administration section of the package insert labeling indicates that the usual adult dosage is 200 mcg/day given either once (2 sprays in each nostril once daily) or twice (1 spray in each nostril twice daily). The Maximum Daily Dose (MDD) is 200 mcg.

C. Basis for Approvability or Not-Approval Recommendation

The ANDA is Approvable for CMC. Bioequivalence, EER, Labeling and MV are pending.

III. Administrative

Following this page, 14 pages are withheld in full.
Chemistry Review #3.

Proposed Expiration Dating Period: Apotex has proposed a tentative 24 month expiration date for their Fluticasone Propionate Nasal Spray 50 ug/spray drug product based upon the stability data presented in their application. The Apotex accelerated and long-term stability data (out to 18 months) supports their proposed expiration dating period.

30. MICROBIOLOGY: N/A.

31. SAMPLES AND RESULTS/METHODS VALIDATION STATUS: Pending.

Note and Acknowledge: Methods Validation package has been sent out concurrent with this chemistry review (sent to Diane Bargo on 4/14/06).

32. LABELING: Satisfactory. Apotex responded on 11/8/05 with a Labeling Amendment, and the labeling was found satisfactory per B. Weitzman/J. Grace on 12/15/05. A new amendment is pending review.

33. ESTABLISHMENT INSPECTION: EER is pending at this time.

34. BIOEQUIVALENCE: Bioequivalence Review is currently pending.

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION: Satisfactory per the C.R. #1.

CC Block

ANDA 77-538
ANDA DUP
DIV FILE
Field Copy
Approvable

Endorsement Block

HFD-625/K.Furnkranz, Review Chemist Kenneth Furnkranz 5/10/06
HFD-625/M.Smela, Team Leader M Smela 5/10/06
F/T by:
V:\FIRMSAM\Apotex\LTRS&REV\77538Rev03kjf.doc
STATUS/TYPE OF LETTER: Chemistry Completed. Pending Bioequivalence EER & MV

Add #1

15.1

CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

ANDA 77-538

Fluticasone Propionate Nasal Spray, 50 ug/Spray

Apotex Inc.

Kenneth J. Furnkranz
Division of Chemistry 1

Addendum #1 to Chemistry Review #3

CDER **CHEMISTRY REVIEW TEMPLATE** CDER

Chemistry Assessment Section

ANDA 77-538
Addendum #1 to Chemistry Review #3

Status of the ANDA as of the Chemistry Review #3: ANDA #77-538 was Approvable for CMC with EER, Methods Validation, Labeling and Bioequivalence pending.

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	**Acceptable**	7/26/06	S. Adams
Methods Validation	**Pending**		
Labeling	**Pending**		B.Weitzman/J.Grace
Bioequivalence	**Incomplete (pending DSI "for cause" Inspection)**	**8/22/06**	**Nguyen/Makary/B. Davit**
EA	Acceptable	10/24/05	K.Furnkranz
Radiopharmaceutical	N/A		

July 18, 2006: Gratuitous Chemistry Amendment: On July 18, 2006 Apotex submitted a gratuitous amendment requesting to withdraw (b) (4), (b) (4) as a contract testing facility. (b) (4) was added as a contract testing laboratory to their ANDA as a result of the request by FDA to include a test for (b) (4) to their specifications for the drug substance (this test was in the current USP monograph). Apotex added the contract testing facility to perform the (b) (4) test. However, in a 2006 PF in-process revision announcement, the (b) (4) test was deleted from the monograph. As a result, Apotex has deleted (b) (4) from their ANDA. Apotex that provided an updated list of facilities utilized by them for this ANDA.

A new EER was submitted to the Office of Compliance with (b) (4) deleted from the request. The EER was found acceptable for all of the other firms listed per S. Adams on 7/26/06.

Conclusions and Recommendations: ANDA is Approvable for CMC. Bioequivalence (DSI "for cause" inspection), Labeling and Methods Validation are pending.

A. Reviewer's Signature:

Kenneth J. Furnkranz

Date Completed: 9/13/06

CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

CC Block

ANDA 77-538
ANDA DUP
DIV FILE
Field Copy
Approvable

Endorsement Block

HFD-625/K.Furnkranz, Review Chemist 9/13/06
HFD-625/M.Smela, Team Leader M Smela 9/14/06
F/T by:
V:\FIRMSAM\Apotex\LTRS&REV\77538Rev03Addendum#1kjf.doc
STATUS/TYPE OF LETTER: Chemistry Completed. Pending Bioequivalence, Labeling & Method Validation

The (b) (4) test remains in the USP monograph and in the applicant's specification and they are responsible for it until officially deleted in USP. PF is not official.
M Smela 9/14/06

CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

ANDA 77-538

Fluticasone Propionate Nasal Spray, 50 ug/Spray

Apotex Inc.

Kenneth J. Furnkranz
Division of Chemistry 1

Addendum #2 to Chemistry Review #3

CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

ANDA 77-538
Addendum #2 to Chemistry Review #3

Status of the ANDA as of the Chemistry Review #3, Addendum #1 on 9/4/06:
ANDA was Approvable for CMC with Labeling and Bioequivalence pending.

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	7/26/06	S. Adams
***Methods Validation**	**Pending**	**8/1/06**	**E. Walker/ HFR-NE560**
Labeling	Acceptable	10/25/06	C.Hoppes/J.Grace
****Bioequivalence**	**Incomplete (DSI Inspection)**	**8/22/06**	**Nguyen/Makary/B. Davit**
EA	Acceptable	10/24/05	K.Furnkranz
Radiopharmaceutical	N/A		

* - NERL performed methods verifications for the following tests: Assay (content (b) (4)

Note: Additional methods were listed for validation. The Division of Field Science assigned portions of the MV to NERL and DPA (St. Louis). DFS has been contacted regarding the status of the additional methods (PSD, DSD, Spray Pattern). Tom Savage of DFS will check and inform us of the current status of the outstanding evaluations at DPA. The Method Validaion is still pending at this time.

** - **The Bioequivalence Status is as follows:**

- The Statistical Bioequivalence review is in DFS.
- The In-Vitro Equivalence studies conducted by Apotex are acceptable on 8/22/06 (file in V:\firmsam\apotex\ltrs&rev\77538a0706.doc).
- The In-Vivo Bioeqivalence study has also been found acceptable (file in V:\ firmsam\apotex\ltrs&rev\77538a0205.doc.) The application is incomplete

pending the results of a "for cause" DSI inspection of the laboratory which performed the clinical study.
- The review of the clinical portion is also pending.

Cause for Addendum #2 to C.R. #3: Addendum #2 was prepared as a result of the annual update submission by (b) (4) to their DMF # (b) (4) for the manufacture of (b) (4) on December 21, 2006. The (b) (4) DMF was reviewed by this reviewer and found adequate on 7/11/07 for the manufacture of (b) (4)

New Chemistry Amendments: No new Chemistry Amendments have been submitted as of this date (Electronic Document Room checked 7/18/07).

USP Monograph Changes: USP 30 Supplement 1 (effective 8/1/07) widens the Fluticasone Propionate assay and deletes the residual (b) (4) test. These changes do not have an effect on the ANDA.

Special Note: A new monograph for Fluticasone Propionate Nasal Spray will become official in USP 30 Supplement 2 (effective 12/1/07). Apotex will need to update their ANDA reflecting the inclusion of the drug product monograph into the USP once the monograph becomes official..

Conclusions and Recommendations: The ANDA is Approvable for CMC. Bioequivalence and MV are pending.

Reviewer's Signature: **Date**

CC Block

ANDA 77-538
ANDA DUP
DIV FILE
Field Copy

Endorsement Block

HFD-625/K.Furnkranz, Review Chemist
HFD-625/M.Smela, Team Leader
F/T by:
V:\FIRMSAM\Apotex\LTRS&REV\77538Rev03Addendum#2kjf.doc
STATUS/TYPE OF LETTER: Chemistry Completed. Pending Bioequivalence Review/DSI Inspection and MV.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kenneth Furnkranz
7/23/2007 03:12:19 PM
CHEMIST

Michael Smela
7/23/2007 03:39:32 PM
CHEMIST
The ANDA may be approved when BE is OK provided DMF (b) (4) remains OK, no new cmc info submitted and the pending MVP (DPA) is not returned with adverse comment. A USP monograph for the DP is effective 12/1/07 and amendment needed if not approved by then.